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OCTOBER, 1931

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second-Class Matter, July 10, 1925, at the Postoffice at Chicago, Illinois, Under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of Oct. 3, 1917, authorized July 29, 1920.

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ARCHIVES OF SURGERY

VOLUME 23 OCTOBER, 1931 NUMBER 4

THE NATURE AND ORIGIN OF SYNOVIAL FLUID*

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The conception of the synovial membrane as an endothelium or epithelium designed to secrete the synovial fluid was challenged by Hueter [1] in 1866. By the method of silver impregnation he demonstrated interspaces between the synovial cells filled by collagenous fibers which, in some places, covered the upper surface of the membrane. After thirty years of controversy, Hueter's views were brought to general rocognition by Braun [2] and Hammer.[3] The majority of recent investigators regard the synovial membrane as a modified connective tissue. This theory, however, makes the origin of the synovial fluid problematical. Of the various explanations advanced, none is supported by sufficient evidence.

This study deals with the phenomena of precipitation, the viscosity, the specific gravity and the mucinous substance of synovial fluids. Different fractions were separated and analyzed. By correlation of the data, an effort was made to determine the source and composition of the synovial fluid. Some clinical applications are outlined.

1. PRECIPITATION PHENOMENA (SACK FORMATION)

A simple test to differentiate between transudates and exudates was devised by Primavera and Rivalta.[4] A drop of the unknown fluid is permitted to fall into a test tube with 3 per cent acetic acid. Plasma and transudates cause a faint trace while exudates produce a turbidity like cigaret smoke, which is regarded as a positive reaction. Effusions

* Submitted for publication, Dec. 30, 1930.

* Read in part before the Pathological Conference, Oct. 24, 1930.

* From the services of Dr. Harry Finkelstein and Dr. Samuel Kleinberg, Hospital for Joint Diseases.

1. Hueter: Zur Histologie der Gelenkflächen und Gelenkapseln mit einem kritischen Vorwort über die Versilberungsmethode, Virchows Arch. f. path. Anat., 1866, vol. 36.

2. Braun, H.: Untersuchungen über den Bau der Synovialmembran und Gelenkknorpel sowie über die Resorption flüssiger und fester Körper aus der Gelenkhohle, Deutsche Ztschr. f. Chir., 1894, vol. 39.

3. Hammer, J.: Ueber den feineren Bau der Gelenke, Arch. f. mikr. Anat. **43**:266 and 813, 1894.

4. Primavera and Rivalta, in Sahli: Diagnostic Methods, ed. 2, Philadelphia, W. B. Saunders Company, 1918, p. 917.

of the pleural and peritoneal cavities and the contents of hydrocele and serous ovarian cysts give either a positive or a negative Rivalta reaction (fig. 1, tubes *b* and *e*).

Normal and the great majority of pathologic synovial fluids, however, behave differently. The drop does not disperse immediately in the acid solution, but forms a membrane that envelops the contents like a sack (fig. 1, tubes *a*, *c* and *d*). This formation may float on the surface like a balloon, or sink to the bottom of the test tube. A great number of synovial fluids form a sack that sinks to a certain depth and is connected by a tube to the surface. The membrane can be very resistant, in which event the sack is permanent. Figure 2 shows a sack

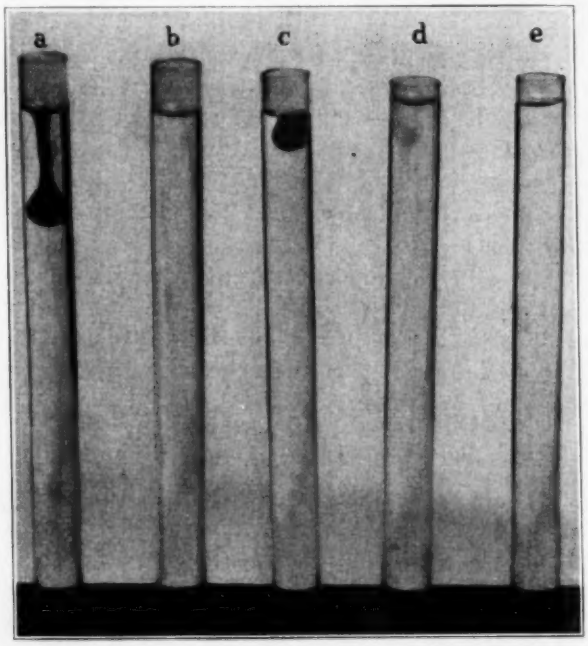

Fig. 1.—*a* and *c* show sack and tube formation; *b*, streaks of turbidity; positive Rivalta reaction in a pleural effusion; *d*, a very thin sack in synovial fluid, and *e*, perfectly clear fluid; negative Rivalta reaction in a serous ovarian cyst.

preserved for months. Other fluids form thin membranes through which diffusion takes place rapidly and which disappear in a short time. The diffusion of hemoglobin into the acid can be nicely observed in hemorrhagic fluids. When the acid solution diffuses into the sack, a secondary membrane is sometimes formed.

The behavior of the sack depends on the concentration of the acid used and the character of a given fluid. Table 1 gives a summary of the conditions of sack formation in various concentrations of acetic and hydrochloric acid. The former causes sacks to form in concentrations

from glacial to 0.25 per cent, in the latter, in from twentieth-normal to two hundredth-normal solutions.

Table 2 shows that a maximum dilution of 1 : 10 with water still can result in sack formation. With serum, the maximum dilution was 1 : 4. Water tends to keep the sack on the surface, while serum, owing to its higher specific gravity, favors falling and dispersion. This will explain differences when, later, saliva and synovial fluid are compared.

TABLE 1.—*Sack Formation in Acids*

Acid	Characteristics
Glacial acetic	Unstable, quickly torn
50% acetic	Thin, swims on surface
50 to 5% acetic	Remains on surface
5 to 1% acetic	Sack and tube formation
1 to 0.25% acetic	Thin, stringy tubes
Concentrated to tenth-normal hydrochloric acid (0.001%)	No sacks
Twentieth-normal hydrochloric acid	Sack sinks to bottom
Fortieth-normal hydrochloric acid	Sack floating, then sinking
Eightieth to two hundredth-normal hydrochloric acid	Tube formation
Two hundredth-normal hydrochloric acid	No sack formation

TABLE 2.—*Maximal Dilution of Ten Synovial Fluids with Water and Serum Giving Sack Formation*

		Cases
Dilution with water	1:3	1
Dilution with water	1:5	6
	1:10	3
Dilution with serum	4:6	1
	1:1	1
	1:4	1

TABLE 3.—*Sack Formation in Effusions from Two Hundred Joints (One Hundred and Twenty-Two Inflammatory and Seventy-Eight Traumatic) and in Fluids from Thirteen Normal Knee Joints at Autopsy or Operation*

	Pathologic Fluids		Normal Fluids	
	Cases	Per Cent	Cases	Per Cent
Sack formation: positive	188	94	13	100
negative	12	6	0	0
Rivalta reaction: positive	8	4	..	...
negative	4	2	..	...

Sacks were produced in the original fluids as well, but they were extensively studied in the clear filtrate after separation of cellular sediment by centrifugation.

Table 3 gives a review of my studies on sack formation. Fluids obtained from thirteen normal joints following amputation or at operation were positive for sack formation. In the effusions of two hundred inflammatory and traumatic joints, sack formation was present in 94 per cent and absent in only 6 per cent. Of the latter, 4 per cent gave positive and 2 per cent negative Rivalta reactions.

In the twelve cases in which sacks did not form, the following diagnosis was made: chronic prepatellar bursitis (housemaids' knee), seven cases; chronic nonspecific arthritis, four cases (one of these fluids was obtained at operation, and it is likely that there was an admixture of serum), and ganglion of the wrist, one case (this fluid was aspirated previously and contained numerous cells, with 90 per cent polymorphonuclear leukocytes).

Sacks Containing Acid in the Synovial Fluid.—By reversing the arrangement of the experiment, membranes can be produced which enclose the acid solution. A small test tube is half filled with synovial fluid; a drop of methyl orange is added. Most synovial fluids, being

Figure 2

Figure 3

Fig. 2.—Sack which has been preserved for two months is seen floating at the top of the tube.

Fig. 3.—Sack and tube containing hydrochloric acid which was dropped into synovial fluid.

slightly alkaline, take a yellow tint by this indicator. Several drops of 10 per cent hydrochloric acid are let fall into the tube. The specific gravity of the acid at this concentration is around 1.050 and exceeds the gravity of synovial fluids, as shown in table 11. The hydrochloric acid therefore sinks, enveloped in a membrane which forms a tube and a sack at the bottom. While the rest of the fluid remains yellow, the contents of the tube and the sack change to red, which proves that they contain the hydrochloric acid. When the tube is allowed to stand, diffusion takes place through the membrane. This causes the sack to rise to a higher level, and finger-like protusions branch out from it (fig. 3). Gradually the

distinct structures disappear and a loose meshwork fills the tube. The binding of acid is permanent. The contents never take the red color observed in plasma, transudates and exudates. In these fluids, the acid sinks freely, the whole fluid changes quickly to red, and a pinkish precipitate accumulates at the bottom.

The precipitation of synovial fluid by alcohol also has a characteristic appearance. A drop of synovial fluid let fall into a tube with absolute alcohol sinks to the bottom leaving threads throughout the fluid and a mushy precipitate at the bottom (fig. 4), which looks like a bulb and

Fig. 4.—Mushy precipitate produced by dropping synovial fluid into absolute alcohol.

roots, and represents an effort at sack formation, prevented by the excessive dehydrating action of the alcohol. No changes occur if the tube is allowed to stand for weeks. Serum, transudates and exudates form a precipitate which falls quickly to the bottom, the alcohol remaining clear.

Sack formation is also observed when a drop of synovial fluid is let fall into a concentrated solution of corrosive mercuric chloride; sacks containing the sublimate solution are obtained by dropping the corrosive mercuric chloride into the synovial fluid.

Microscopic Appearance.—Under low magnification the membranes appear to consist of bundles and threads running in different directions and forming a meshwork. Under high magnification, minute granules are seen to fill the meshes. The structures resemble the inner shell of a hen's egg.

Comment.—On the basis of the conception of the synovial membrane as a connective tissue, the theory was widely accepted that synovial effusions are derived from the circulation.

This study of precipitation, however, has demonstrated peculiar precipitation phenomena differing from the reactions that occur in either transudates or exudates. Not only most effusions from inflammatory joints, but even the hemorrhagic effusions are positive for sack

TABLE 4.—*Comparative Reactions of Blood Serum, Synovial Fluid, Egg White and Saliva to Precipitation by Various Agents*

Reagent	Serum	Synovial Fluid	Egg White	Saliva
Water	Clear	Clear	Turbid	Clear
Acetic acid	Precipitation	Sack	Sack	Sack
Hydrochloric acid	Precipitation	Sack formed between 20th and 200th normal hydrochloric acid	Sack	Sack
Hydrochloric acid 10% overlaid	Precipitation	Sack	Sack	Sack
Alcohol	Granules	Threads	.....	.....
Alcohol overlaid	Precipitation at border	Precipitation	.....	.....
Nitric acid	Precipitation	Precipitation	Precipitation	Precipitation
Boiling	Curd	Curd	Curd	Turbid
Potassium hydroxide	Clear	Clear	Jelly	Clear

formation. They therefore do not consist simply of blood corpuscles and plasma, but must contain at least one component not derived from the circulation. This substance that produces the characteristic precipitation phenomena is, on the other hand, also present in normal synovial fluids.

The next step in this investigation was a search for other body fluids which give identical precipitation reactions.

Sack formation was found to be positive in saliva and egg white. The sacks in both of these substances swim on the surface of the 3 per cent acetic acid solution and are transparent. Table 4 gives a review of the comparative reactions. Both saliva and egg white are products of cell secretion and not of extravasation. Both are viscous fluids containing a mucinous substance. Synovial fluids have similar properties. The study of viscosity and the mucinous substance was therefore undertaken.

2. VISCOSITY

Data on the viscosity of synovial fluids have been recorded only by Schneider [5] and by Cajori and collaborators.[6] I shall therefore analyze and compare my material with the observations of these authors and then follow up clues uncovered by this study which may lead to the source of synovial fluid.

The specific or relative viscosity was determined in seventy fluids from sixty-five patients (table 5). Fifty specimens were aspirated from inflammatory effusions in forty-seven cases of acute and chronic specific and nonspecific monarticular or polyarticular arthritis and bursitis. The diagnosis was made on the basis of clinical findings, roentgenograms, bacteriologic, serologic and cytologic studies and estimations of bilirubin in the fluids.

Twenty fluids of traumatic origin were obtained from eighteen patients. The history of injury was confirmed by the hemorrhagic

TABLE 5.—*Summary of Determinations on the Viscosity of Synovial Fluid*

Joints	Inflammatory Cases*	Traumatic Cases†
Knee	38	13
Prepatellar bursitis	4	4
Ankle	2	1
Wrist	2	0
Elbow	1	0
Total	47	18

* One case was aspirated three times and one twice.
† Two cases were aspirated twice.

character, the presence of fat and bone marrow cells or the high icteric index of the effusions, as I have pointed out in a series of papers.[7] The viscosity was determined on centrifugated clear fluids, with but one exception. This effusion was aspirated from a patient with tuberculous arthritis of the knee. It was milky, contained débris and did not separate on prolonged centrifugation. The viscosity was 18.

The Hess viscosimeter was used, which permits the determination of viscosity up to twenty-eight times that of water at room temperature.

5. Schneider, J.: Untersuchungen über die Viskosität menschlicher Synovia, Biochem. Ztschr. **160**:325, 1925.

6. Cajori, F. A.; Crouter, C. Y., and Pemberton, R.: The Physiology of Synovial Fluid, Arch. Int. Med. **37**:92 (Jan.) 1926. Cajori, F. A., and Pemberton, R.: Chemical Composition of Synovial Fluid in Cases of Joint Effusion, J. Biol. Chem. **76**:471, 1928.

7. Kling, D. H.: Fat in Traumatic Effusions of the Knee Joint, Am. J. Surg. **6**:71, 1929; Bilirubin in Effusions of the Joints, Arch. Surg. **20**:17 (Jan.) 1930; Erythroblasts and Myelocytes in Traumatic Effusions of the Knee Joint, Am. J. Surg. **7**:824 (Dec.) 1929; Wassermann Reaction in Joint Fluids, Am. J. Syph. **13**:596, 1929.

Fluids of a higher viscosity had to be diluted with distilled water. The influence of dilution and the accuracy of the apparatus will be discussed later.

Analysis of the Material.—Fluid was aspirated from the knee joint in 78.5 per cent of the cases (table 5). The viscosity varied in inflammatory effusions from 1.6 to 72 and in traumatic effusions from 2.6 to 34 (table 6). This exceeds by a wide margin the range of viscosity of transudates or exudates and normal secretory products like saliva and egg white (table 7). The largest variation (table 10) is seen in chronic nonspecific arthritis from (1.6 to 72), and the next largest in syphilitic arthritis (from 4.5 to 40.5). Comparatively smaller is the range for gonorrheal arthritis (from 10.1 to 16.8) and tuberculous arthritis (from

TABLE 6.—*Specific Viscosity at 20 C.*

Viscosity	Inflammatory Effusions, Number Fluids	Traumatic Effusions, Number Fluids
1.6 to 5	5	2
5 to 10	6	7
10 to 20	22	6
20 to 30	8	4
30 to 40	3	1
40 to 50	4	0
50 to 72.7	2	0
Total	50	20

TABLE 7.—*Viscosity, Specific Gravity and Sack Formation of Synovial Fluids*

	Number	Specific Viscosity				Specific Gravity	Sack
		1.6 to 5	5 to 10	10 to 20	Over 20		
Inflammatory	50	5	6	22	17	1.018 to 1.032	Positive 44 Negative 6
Traumatic	20	2	6	7	5	1.015 to 1.026	Positive 19 Negative 1

16.6 to 24). One case of rheumatic fever and one of purulent arthritis showed that the viscosity varies at different aspirations during short intervals (from five to seven days) in the same joint.

In the series of traumatic effusions, the cases of prepatellar bursitis showed a smaller range (from 7.9 to 16.1) than the fluids from the knee joints, and two intra-articular fractures showed less variation but higher viscosity (from 13.2 to 22).

Review and Discussion of the Literature.—Schneider devoted his study, published in 1925, to the determination of the viscosity of normal synovial fluid. He aspirated fluid from twenty-nine knee joints of patients who had died from various acute and chronic diseases. Only two showed effusion. He constructed an elaborate apparatus which permitted the examination of minute amounts of the fluid and which registered the highest degrees of viscosity. In the twenty-seven cases

of apparently normal joints, he found a viscosity of from 3.9 to 1,490. Of the two effusions, the viscosity in a case of purulent arthritis was 275.3, and in a case with joint mice, 33.3 The only fluid examined from a living patient was obtained in a case of osteochondritis dissecans; the viscosity was 22.7. The viscosity was highest in cases of sudden death and lower after chronic wasting diseases which had kept the patients in bed, especially tuberculosis, cancer and circulatory disorders. This, Schneider explained by the assumption that resorption of water decreased in the latter cases and by referring to the analysis of synovial fluids of cattle published by Frerichs [8] in 1846. The latter found that the content of solids was about 40 per cent lower and that of water greater in the synovial fluids of new-born calves and fatted cattle than in the synovial fluids of grazing oxen.

TABLE 8.—*Viscosity, Specific Gravity and Sack Formation of Various Fluids*

Fluid	Number	Range of Variation	Viscosity	Specific Gravity	Sack
Normal joint	1	.....	20.00	.....	Positive
Normal joint	1	.....	10.70	.....	Positive
Saliva, filtered	5	±0.20	1.90	1.005	Positive
Saliva, full	2	.....	3.75	.....	Positive
Egg white	4	+1.55 −0.95	5.25	1.040	Positive
Plasma	2	±0.20	2.30	1.027	Negative
Serum	10	+0.50 −0.80	1.90	1.018	Negative
Serum from ovarian cyst	2	+0.80 −0.70	2.20	1.020	Negative
Lymph vesicle in skin	1	.....	2.10	1.012	Negative
Peritoneal	1	.....	1.60	.....	Negative
Pleural	1	.....	1.90	1.022	Negative

On the basis of his observations at autopsy, Schneider estimated that normal synovial fluids have a range of viscosity between 500 and 1,500. Extraordinary as these figures may appear, another observation is still more surprising. He induced the evaporation of 5 per cent of the water content of a fluid, and the viscosity rose from 1,490 to 3,659, an increase of nearly 150 per cent. If that be true, a dilution of 1:1 would depress the viscosity about 3,000 per cent. As has been mentioned, my procedure was to dilute fluids of a viscosity over 28 and to multiply the reading by the volume of water used.

Control examinations were therefore carried out on a series of fluids that had a viscosity under 28. After determination of the viscosity, the fluids were diluted, and the viscosity was registered and multiplied by the volumes of water used. The results in diluted fluids were plus or minus 4.5 per cent; table 9 gives two estimations. The influence of evaporation was also controlled up to 35 per cent. The maximum

8. Frerichs, T.: Die Synovia, in Wagner, R.: Handwörterbuch der Physiologie, 1846, pt. 3, p. 463.

increase over the expected value was 26 per cent. The figures are in good agreement with the experimental curve of the increase of viscosity by protein solutions within the concentrations in synovial fluid, which is given by Hatschek.[9] I have therefore concluded that this calculation is correct within these limits of error, and that the Hess apparatus can be used in a comparative study of the viscosity of synovial fluids. It offers the advantage of having been widely employed in estimations of the viscosity of blood. Less than 0.5 cc. of fluid is needed. The instrument is reasonably priced and comparatively simple to operate. Schade[10] justly pointed out the danger of using new and untried constructions for the determinations of viscosity.

A few precautions are to be observed in carrying out the test. The apparatus should be frequently checked, water in both sides of the capillary being used. The flow of the fluids should be smooth. It is advisable first to work with fluids of low and stable viscosity, for

TABLE 9.—*Effect of Dilution and Evaporation on Viscosity*

Fluid	Viscosity	Per Cent	Difference*
Full fluid I	12.2	100	....
Diluted 1:1	5.6	46	— 4
Full fluid II	6.2	100	....
Diluted 1:1	3.4	55	+ 5
Evaporation 5%	7.2	116	+11
Evaporation 10%	8.0	130	+20
Evaporation 20%	8.8	142	+22
Evaporation 35%	10.0	161	+26

* Difference between expected and obtained viscosity.

instance, with serum. Several determinations should be taken on one fluid, and the average value registered. If the variation exceeds 15 per cent, the apparatus must be cleaned and the water changed and rechecked. For the dilution of synovial fluid, distilled water of room temperature should be used. One per cent is added to the result for each degree above, and subtracted for each degree below, 20 C.

In only two instances in which the joint appeared to be normal did I obtain enough fluid to determine the viscosity. One fluid was secured at operation on a man, 20 years of age, who had suffered from an injury to the internal meniscus a year previously. The viscosity was 20. The second fluid was aspirated from the knee of a leg, amputated for a chronic ulcer after a burn, in a patient 21 years of age. The viscosity was 10.7. The fluids had the same appearance and sack formation as did those from the other ten normal knee joints that I examined at autopsy. Some of the effusions of high viscosity, especially the contents of ganglions, appeared decidedly thicker and more viscid than the

9. Hatschek, E.: Viscosity of Liquids, London, G. Bell & Sons, 1928.

10. Schade, H.: Die physikalische Chemie in der inneren Medizin, ed. 3, Leipzig, Theodor Steinkopff, 1922, p. 562.

material obtained at autopsy. If conclusion is permitted from these cases, I would range the viscosity of normal fluid well within the limits found for the effusions and the two determinations just cited.

Cajori and his associates [6] examined the viscosity of pathologic effusions with the Hess apparatus. Their data, recorded in two papers, can therefore be directly compared with my material. In an article on the physiology of the synovial fluid that appeared in 1926, Cajori, Crouter and Pemberton gave the viscosity in nine cases. One fluid was from a patient with traumatic synovitis; viscosity 3.3. The remaining eight were obtained from cases of chronic arthritis, the etiology of which could not be defined. The viscosity varied from 2.7 to 16.7. The authors did not comment on their observations. These data are in agreement with my material. Even in so limited a number, the wide range of variation exceeds decidedly the limits of transudates, exudates and other secretions. In the second paper, by Cajori and Pemberton, in which the chemistry of the synovial fluids is dealt with, the viscosity in twelve effusions is registered. One fluid (case 10) was from a patient with villous arthritis, and had a viscosity of 4.78; another (case 5) was from a patient with anasarca, and had a viscosity of 4.71. No diagnosis was given in the remaining ten cases, which had a range of viscosity between 2.91 and 4.79. The difference between the maximum and minimum viscosity was only 1.88 and forms a contrast to the extremely high values of Schneider. The authors calculated an average viscosity of 4, next to their average for plasma. This is apt to be misleading. Simple observations show the wide difference in fluidity and stickiness of fluids within joints which is not commonly met with in plasma. Here an average represents a nearly uniform property. In the fluids of joints, however, it only indicates an artificial condition caused by a limited selection of the material, most likely owing to a mistake in the technic of aspiration. It is frequently noticed that thin needles are used. Therefore, only effusions of low viscosity are obtained; when the fluid is thick, the aspiration will not be successful. This also explains why some physicians, after attempting without success to aspirate traumatic effusions, maintain that the blood is coagulated in the synovial cavities, while really only small coagula form, and the bulk of the blood remains fluid but of thick consistency through an admixture of synovial secretion. It is therefore essential to employ thick needles in aspirating fluids from joints.

Factors Responsible for Viscosity.—The degree of inflammation and the stage of the process are of importance, irrespective of etiology. For this reason fluids from patients with acute specific and nonspecific arthritis show less variation and start from a higher level than effusions from patients with chronic disease (table 10). In the four cases of gonorrheal arthritis showing the smallest variation, the fluids were aspi-

rated within five weeks after the onset of symptoms. The lowest values were found in chronic hydrops, without involvement of the structures of the joints, and the highest were registered in hypertrophic arthritis and thickened bursae when only a few cubic centimeters of fluid was obtained. Roentgenograms confirmed the fact that no further accumulation of fluid was present in these cases.

The influence of these factors was pronounced in the group of syphilitic cases. Although of uniform etiology, they were in different stages. The lowest viscosity of 4.5 was found in a child, 5 years of age, with congenital syphilis, in whom effusion of the knee joints had developed two weeks previous to examination. Thirty cubic centimeters of fluid was aspirated from each joint. The highest viscosity, 40.8, was found in a case of dactylitis and tenosynovitis of the wrist of two years' duration which yielded only 2 cc. of fluid. Another case of

TABLE 10.—*Relation of Viscosity to Types of Arthritis*

Inflammatory	Cases	Viscosity	Traumatic	Cases	Viscosity
Nonspecific arthritis, acute and subacute*	11	12 to 32	Synovitis, knee	11	2.6 to 34
Chronic†	22	1.6 to 72	Intra-articular fracture, knee	2	13.2 to 22
Syphilitic	5	4.5 to 40.8	Prepatellar, bursitis	4	7.9 to 16.1
Tuberculous	3	16.6 to 24	Synovitis, ankle	1	20
Gonorrheal	4	10.1 to 16.8	.....	..	.....
Rheumatic fever (3 determinations)	1	7.8 to 12	.....	..	.....
Purulent arthritis (Staphylococcus aureus, positive; 2 determinations)	1	6 to 16.2	.....	..	.....

* Streptococcus positive in four cases.
† Streptococcus positive in three cases, and staphylococcus positive in one case.

syphilitic hydrops of the right knee, of thirteen years' duration, from which 50 cc. of fluid was obtained, showed a viscosity of 11.4.

The wide range of viscosity points to differences in the physicochemical composition of synovial fluid in need of investigation.

3. SPECIFIC GRAVITY

The specific gravity of body fluids is determined by the concentration of crystalloids and colloids. According to Ruess,[11] the specific gravity of plasma and that of effusions is approximately proportional to their content of proteins.

This same relation was found also by Horyi,[12] in twenty-five synovial fluids obtained at autopsy on patients with general edema due to disorders of the circulation and kidneys. The specific gravity varied from 1.003 to 1.818. The lowest specific gravity was associated with an albumin content of about 0.5 per cent, and the highest (1.018) with

11. Ruess, cited in Sahli: Diagnostic Methods, ed. 2, Philadelphia, W. B. Saunders Company, 1918, p. 917.

12. Horyi, K.: Ueber die menschliche Synovia, Virchows Arch. f. path. Anat. **251**:649, 1924.

one of 3.9 per cent. For normal synovial fluids, a specific gravity of 1.040 was given by Mayeda.[13] He did not state the number or source of the fluids.

In only three cases of effusions into the joints was the specific gravity registered. In two cases of synovitis of the knee, Hammarsten[14] found a specific gravity of 1.017 and 1.022, respectively. In a case of coxitis, Salkowski[15] registered a value of 1.021.

I tested twenty-five inflammatory and fifteen traumatic effusions for specific gravity. When sufficient fluid was at hand the estimation was carried out with the urinometer; otherwise, a modification of Hamerschlag's drop method in the determination of the specific gravity of blood was used (Kirkpatrick and Kling[16]). A water-insoluble mixture with a specific gravity of 1.020 is made up by combining one part of carbon tetrachloride and three and a half parts of xylene in a test tube. A drop of synovial fluid is let fall into the mixture. If it sinks to the

TABLE 11.—*Specific Gravity*

Specific Gravity	Inflammatory Effusions		Traumatic Effusions	
	Cases	Per Cent	Cases	Per Cent
1.015 to 1.020	7	28	5	33.5
1.021 to 1.025	13	52	8	53.5
1.026 to 1.030	4	16	2	13.4
1.032	1	4	0	....
Total	25		15	

bottom, its specific gravity is higher, and the heavy carbon tetrachloride is added slowly until the drop is fixed about midway in the fluid. If the drop floats on the surface, the specific gravity is depressed by the addition of the lighter xylene until it again comes down half way.

Over 50 per cent of both groups had a specific gravity between 1.021 and 1.025 (table 11). These values are also commonly found in exudates. About 30 per cent showed lower values and were in the range of those for serum or transudates. Only about 15 per cent had a gravity over 1.025, but they did not exceed the values for plasma. The striking differences in viscosity were therefore not reflected by the specific gravity. There was no correspondence between these properties; the

13. Mayeda, Tomosuke: Experimentelle histologische Studie über die Synovialmembran, Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo **21**:393, 1919-1920.

14. Hammarsten, O.: Beiträge zur Chemie der Synovia, Jahresb. Thier-Chemie **12**:480, 1881-1882.

15. Salkowski, E.: Zur Kenntnis der Synovia, insbesondere des mucinähnlicher Körpers derselben, Virchows Arch. f. path. Anat. **131**:304, 1893.

16. Kirkpatrick, J., and Kling, D. H.: A Simplified Method for Determination of the Specific Gravity of a Few Drops of Urine, J. A. M. A. **87**:487 (Aug. 14) 1926.

highest specific gravity, 1.032, was registered with a viscosity of 8; on the other hand, an effusion with a specific gravity of 1.019 had a viscosity of 43.

The concentration of the proteins that determines the specific gravity is, therefore, not the underlying cause of the variation in viscosity and the striking precipitation phenomena (sack formation). A review of the data published on the protein content of synovial fluids shows that it ranges between 0.5 per cent (Horyi [12]) and 7.25 per cent (Cajori and his associates [6]). If only the pathologic local effusions of the joints are considered, the range narrows from 3.5 to 7.25 per cent (Allison and his associates [17]), a difference of not more than 100 per cent, and is within the values for exudates and plasma.

The Diffusible Constituents.—Nonprotein nitrogen was found in equal concentration in plasma and synovial fluids by Fremont-Smith,[18] Allison [17] and Cajori [6] and their co-workers. Cajori found also the amino-acids, urea nitrogen and carbon dioxide in synovial fluid to be in close approximation to the values for plasma.

Of the inorganic salts, calcium was found to vary from 4.6 to 9.4 mg. per hundred cubic centimeters in the material of Horyi, but no relation existed between the concentration of the calcium and protein and the specific gravity. Lesser variations from 8.3 to 10.7 mg. were reported in three cases by Cajori and his co-workers. In six fluids from patients with chronic nonspecific arthritis I found a range in calcium from 7.8 to 10.6 mg. per hundred cubic centimeters.

Salkowski first recorded the high content of 772 mg. of sodium chloride in his case. In comparative studies of joint fluids and plasma, Fremont-Smith, Allison and Cajori and their associates demonstrated the sodium chloride content to be higher in the former. The maximum difference of 54 mg. was found in Cajori and Pemberton's case 8, the sodium chloride in the plasma being 549 as opposed to 604 mg. per hundred cubic centimeters in the synovial fluid. In two patients of my series during a period of fasting, the chlorides were estimated in plasma and synovial fluids. The first had chronic synovitis which had developed after trauma to the right knee. Chlorides in the plasma amounted to 447 mg., and in the synovial fluid, to 562 mg. (a difference of 115 mg.). The second patient had hypertrophic arthritis with free bodies in the right knee; the amount of chlorides in the plasma was 472 mg., and in the fluid, 582 mg. (a difference of 110 mg.). Phos-

17. Allison, N.; Fremont-Smith, F.; Dailey, M. E., and Kennard, M.: Comparative Studies Between Synovial Fluid and Plasma, J. Bone & Joint Surg. **8**: 758, 1926.

18. Fremont-Smith, F., and Dailey, M. E.: Studies in the Distribution of Chloride and Protein Between Plasma and Synovial Fluid, J. Biol. Chem. **70**:779 1926.

phorus was estimated in the fluid from five patients with atrophic and hypertrophic arthritis. The values ranged between 3 and 3.9 mg. per hundred cubic centimeters. The sugar content of synovial fluids in noninfected cases was found by Fremont-Smith, Allison and their associates to vary between 58 and 119 mg. per hundred cubic centimeters. In ten fasting patients, the average value of sugar was 96 mg. in plasma and 84 mg. in synovial fluid, a difference of about 13 per cent. In fifteen nonpurulent cases reported by Cajori and his co-workers, the concentration was between 68 and 132 mg. per hundred cubic centimeters; however, these patients were not fasting, and the authors demonstrated the rise in the concentration of sugar with the ingestion of food.

In two tuberculous effusions, Allison and his associates found values for sugar of 45 and 61 mg., and in four fluids positive for gonococci and streptococci, the sugar was between 19 and 43 mg. The authors

TABLE 12.—*Cell Count and Sugar Content*

No.	Diagnosis	Cells	Polymorphonuclear Leukocytes, per Cent	Sugar, Mg. per 100 Cc.	Comment
1	Synovitis, knee	27,800	74	67	Trauma two years previously
2	Gonorrheal polyarthritis	26,100	86	70	Acute
3	Syphilitic bilateral arthritis, knee	18,300	66	99	Acute; congenital syphilis
4	Chronic syphilitic arthritis, knee	5,450	5	130	
5	Atrophic polyarthritis	4,500	22	92	Subacute
6	Traumatic synovitis, knee	2,300	65	123	Erythrocytes, 3,300,000
7	Chronic atrophic polyarthritis	1,800	46	105	
8	Chronic arthritis, knee	1,400	68	96	Nonspecific
9	Synovitis, knee	900	2	94	Blood sugar at fasting, 82
10	Hypertrophic arthritis, knee	700	3	81	Blood sugar at fasting, 71

concluded that very low values may be indicative of bacterial infection. However, Cajori and Pemberton reported a case of purulent synovial fluid of unknown etiology in which the sugar was almost absent (from 8 to 10 mg.), and in which repeated cultures and inoculation in animals gave negative results. The cell count amounted to 13,880, of which 97 per cent were polymorphonuclear leukocytes. They carried out a glycolysis experiment on this fluid and on the cell-free filtrate by adding 30 mg. of dextrose to each portion. After incubation for seventeen hours, the full fluid showed a decrease in the sugar content from 145 to 27 mg., while the centrifugated specimen showed a decrease only from 121 to 114 mg. per hundred cubic centimeters. The authors concluded that glycolysis is due to the action of the leukocytes, irrespective of bacterial infection.

Some support is given to this conclusion by ten effusions of specific and nonspecific origin (table 12). The total cell count seems to have less influence on the glycolysis than the number of leukocytes present. Number 4 with 5,450 cells but only a few leukocytes had 130 mg. of sugar, while number 8 with only 1,400 cells had 68 mg. of sugar per

hundred cubic centimeters. In this case, however, the polymorphonuclears amounted to 68 per cent. Fluid from these patients was aspirated in the afternoon and evening, and, therefore, the influence of the intake of sugar must be considered. In two patients (9 and 10) with noninfectious chronic arthritis (one posttraumatic, the other hypertrophic), sugar was estimated in the synovial fluids and blood which were simultaneously aspirated before breakfast. The synovial fluids contained, respectively, 94 and 81 mg. of sugar per hundred cubic centimeters. The sugar in the plasma was 82 and 71 mg., respectively. It can be seen, therefore, that in the fasting state, the sugar in the synovial fluids exceeded the sugar in the plasma, both patients' total cell counts were low, and the polymorphonuclear leukocytes were only from 2 to 3 per cent. It can be concluded that accurate information is obtained only if the estimation for sugar is carried out simultaneously on the plasma and synovial fluid of the fasting patient. According to Fremont-Smith and his associates, lower values for protein and higher values for chloride are found in pleural, peritoneal and spinal fluids, as well as in synovial effusions, than in plasma; in fact, this is true of all body fluids that are produced by dialysis. On the basis of their calculations, these authors found that the Donnan membrane equilibrium applies to the distribution of protein and chloride between synovial fluid and plasma. They concluded that pathologic effusions into the joints are derived from plasma by dialysis rather than by secretion. This theory will be discussed later.

Important as the rôle of the diffusible constituents may otherwise be, it has no significance in an explanation of the variation in viscosity and sack formation in synovial fluids. This is realized when one figures in percentages rather than in milligrams.

The highest value of sugar encountered does not exceed 0.15 per cent; that of sodium chloride is less than 0.8 per cent. In these concentrations neither has an influence on viscosity. According to Heyder and Rohrer,[19] a solution containing salts and urea in the concentration of the blood has a viscosity of only 1.018.

Carbon dioxide increases the viscosity of fluids. However, Cajori and his associates found in synovial fluid a carbon dioxide percentage by volume of from 43 to 61, which is under the low reading for venous blood plasma.

Increased acidity may be responsible for a raise in viscosity. In an excellent review of the data on synovial fluids, Forkner [20] tabulated the p_H values according to different authors. For nonpurulent, inflammatory and traumatic fluids, the range of p_H is from 6.91 to 8.4. The

19. Heyder and Rohrer: Deutsches Arch. f. klin. Med. **121**:221, 1916.

20. Forkner, C. E.: The Synovial Fluid in Health and Disease with Special Reference to Arthritis, J. Lab. & Clin. Med. **15**:1187, 1930.

extreme values were obtained in few cases. In seven purulent, septic cases registered by Boots and Cullen, Cajori and Pemberton and Habler, the p_H ranged from 6.19 to 7.24. Hammarsten, Mayeda and Horyi found the reaction in their cases to be alkaline.

In thirty fluids in my material, from patients with acute and chronic, nonspecific, gonorrheal and syphilitic arthritis, the reaction to litmus was alkaline. One fluid, from the knee of a child with acute purulent arthritis, caused by injury through the driving in of a nail, gave an acid reaction. *Staphylococcus aureus* was present in great numbers in the smears and was readily grown in the cultures. However, on the day following the operation the reaction had already changed to alkaline. The viscosity dropped from 16 to 6.

TABLE 13.—*Reactions of Mucin, Mucoid and Nucleoproteins*

Substance	Origin	3 Per Cent Acetic Acid Precipitin	Reduction of Copper Sulphates	Phosphorus
Mucin	Saliva	Heavy	Positive	Negative
Pseudomucin	Ovarian cyst	Negative	Positive	Negative
Ovomucoid	Egg white	Slight	Positive	Negative
Chondromucoid	Cartilage	Positive	Positive	Negative
Synovia mucin (von Hoist [22])	Synovial fluid	Positive	Positive	Negative
Synovin (Salkowski [15])	Synovial fluid	Positive	Negative	Negative
Nucleoprotein	Nuclei cyto-globin	Positive (soluble in excess)	Negative	Positive

TABLE 14.—*Specific Gravity of Full and Supernatant Synovial Fluid* *

No.	Full	Supernatant	Expected Value
1	1.022	1.018	1.016
2	1.022	1.017	1.016
3	1.023	1.018	1.016
4	1.026	1.013	1.013

* The specific gravity of the acetic acid used for precipitation was 1.004.

Therefore, as first brought out by Boots and Cullen,[21] an acid reaction is found only in purulent arthritis. The p_H of nonpurulent fluid is within the range or exceeds the values of normal plasma.

The review shows that neither the total percentage of protein nor any of the diffusible constituents can explain the differences in the viscosity and precipitation phenomena of synovial fluids. It is therefore necessary to consider the different fractions of the proteins separately.

Globulins.—That globulin increases viscosity more than does albumin was stated by Heyder and Rohrer and experimentally proved in the curves quoted by Hatschek. The globulin content estimated by Cajori

21. Boots, R. H., and Cullen, G. E.: The Hydrogen Ion Concentration of Joint Exudates in Rheumatic Fever and Other Forms of Arthritis, J. Exper. Med. **36**:405, 1922.

and Pemberton in twelve fluids varied from 0.3 to 3.45 per cent. A case of anasarca had the minute amount of 0.025 per cent. With the exception of one case, the corresponding content in the plasma was found to be higher. The ratio of albumin to globulin was 2 in the fluids and 1.9 in the plasma. In other words, in this material globulins made a smaller percentage of the total proteins than they did in plasma, with one exception. They can therefore not be responsible for the higher viscosity of these fluids. However, in fluid from an acute case of gonorrheal polyarthritis, containing 10,200 cells with a protein content of 6.43 per cent, the globulins amounted to 4.18 per cent and the albumin only to 1.31 per cent. The ratio is 0.314. The albumin only makes up 31.4 per cent of the globulins. The viscosity in this case was 16.8 (table 15).

The influence of the globulins was therefore determined directly by comparing the viscosity of the full fluids and a fraction freed from globulin by precipitation with equal parts of saturated ammonium sul-

TABLE 15.—*Protein Fractions in Synovial Fluid in a Case of Acute Gonorrheal Arthritis*

Fraction	Synovial Fluid	
	Full, per Cent	Supernatant, per Cent
Protein	6.43	5.49
Albumin	1.31	....
Globulin	4.18	3.97
Mucin, calculated	0.94	....
Albumin-globulin	0.314	....

phate. After centrifugation the clear supernatant fluid was pipetted off and the viscosity determined. Since the difference between the viscosity of water and that of the saturated ammonium sulphate was 1.4, half of this number (0.7) was substracted from the viscosity of the globulin-free fraction and the rest multiplied by 2. The last column of number 1 in table 17 shows the decrease in the cited case to be 40.5 per cent. In five other determinations from cases of chronic infectious and noninfectious arthritis, decreases of viscosity between 11.8 and 42.5 per cent are registered. Although this appears to be a considerable percentage, the resulting viscosities still exceed the range for plasma and exudates, with the exception of one case of chronic prepatellar bursitis in which the full fluid has a viscosity of only 2.5 (no. 7 table 17).

The globulins, therefore, have a marked but only a limited influence on the viscosity of synovial effusions.

Fibrinogen.—That the content of fibrin varies in different fluids is demonstrated by the fact that some fluids coagulate completely within a short time after withdrawal; others show only fine threads of fibrin, and a great number remain liquid and clear on standing.

I found that fluids from patients with acute infections coagulated completely and quickly. However, quantitative estimations are needed to draw conclusions that may be of clinical value. As the viscosity is determined after the removal of clots, this variation of fibrinogen in the full fluid is immaterial. An estimate of the fibrinogen in the clear fluid has been attempted in fourteen cases of inflammatory and in eight cases of traumatic effusions by precipitation with equal parts of concentrated sodium chloride solution and incubation in the thermostat.

In the effusions of six cases of traumatic origin and eight cases of inflammatory origin only traces of fibrinogen were found. In two traumatic and six inflammatory effusions very thin floccules appeared, such as those seen in the control made with serum. Fibrinogen therefore was absent or present only in minute quantities in the clear fluids and had no influence on the viscosity.

The result of the investigation reveals that none of the colloids or diffusible constituents of plasma produce the high values, the wide range of viscosity and the precipitation phenomena found in fluids from normal and pathologic joints.

Before considering a component of synovial fluid not found in plasma, the mucinous substance, I shall discuss the relation of viscosity and specific gravity to the sack formation. High viscosity and specific gravity are not essential to such formation. Filtered saliva of a viscosity of only 1.6 shows this phenomenon. In synovial fluids, sack formation occurred at a viscosity of around 3 and at the lowest specific gravity (1.015). Viscosity and specific gravity determine the appearance of the sack. The sacks in saliva and in the fluids of low viscosity are thin and of short duration, while fluids of high viscosity produce sacks with thick membranes which are preserved indefinitely. At low specific gravity the sacks remain on the surface; at higher gravities the tube formation appears and the sacks sink to the bottom. The preservation of the sack depends on the resistance of the membrane and the gravity.

4. THE MUCINOUS SUBSTANCE

In 1846, Frerichs [8] expressed the opinion that the difference in the appearance between transudates and synovial fluid is due to a mucinous substance that can be precipitated by acetic acid. He regarded the synovial membrane as an epithelium, the superficial cells of which undergo disintegration analogous to that of the horny layers of epidermis and form the mucous substance by dissolution in serum.

In 1882, Hammersten [14] examined the mucin in two inflammatory effusions. They contained phosphorus. Therefore, he considered the substance as a nucleo-albumin. Salkowski,[15] in 1893, carefully studied the chemical composition of the synovial fluid in a case of chronic coxitis. The mucinous substance was isolated by precipitation with acetic

acid, redissolution in sodium hydroxide, reprecipitation and repeated washing with alcohol and ether and finally dried in a desiccator over sulphuric acid. The substance amounted to 0.375 per cent. It did not contain phosphorus; after hydrolyzation by boiling with a weak solution of hydrochloric acid for from one to several hours, it did not reduce Trommer's sugar reagent. The absence of phosphorus proved the substance to be different from a nucleoprotein.

A calculation of the figures given by Hammarsten showed that the phosphorus content in the two fluids was only about 0.2 per cent. Nucleo-albumin of such low phosphorus content was not known, and Salkowski concluded that Hammarsten worked with a mixture of mucin and nucleo-albumin derived from the lymphocytes, which were present in these fluids in large numbers.

The absence of a compound nitrogenous sugar was proved by the negative outcome of the Trommer reaction. The mucins being glycoproteins which reduce copper sulphate readily, Salkowski regarded this substance as a special modification of mucin, which he called "synovin."

Von Holst [22] isolated mucin from the synovial fluid of cattle by precipitation with diluted acetic acid in a similar procedure. Examination of the dry product was negative for phosphorus and on hydrolyzation reduced copper salts, thus giving all the reactions of a typical mucin. He made the observation that the supernatant fluid, after precipitation of the mucin, lost its viscous character.

The results obtained by both authors have established in the normal synovial fluids of cattle and the pathologic effusions of man the presence of a mucinous body that is free from phosphorus and therefore not derived from nucleoprotein or cytoglobulin. However, the effusion from a patient with coxitis did not give a positive sugar reaction.

These are the only complete analyses of the mucinous substance in synovial fluid that have been published. This substance was not considered again until 1923 and then in a brief statement by Fisher [23] that the mucin content was 1.95 per cent in normal synovial fluids secured at autopsy on man, and only 0.1303 per cent in oxen. No mention is made of the methods of preparation or analysis, the phosphorus content or the sugar reaction.

The last reference to mucin is found in the article by Cajori and Pemberton.[6] They precipitated the mucin with acetic acid, in the manner of von Holst, removed the supernatant fluid by filtration and determined the nitrogen content either directly or by the loss of nitrogen in an aliquot part of the supernatant fluid. On the basis of von Holst's

22. von Holst, G.: Serosa Mucin; eine Mucinsubstanz im Ascites, Flüssigkeit und Synovia, Ztschr. f. phys. Chem. **43**:145, 1904-1905.

23. Fisher, A. G. T.: Physiological Principles Underlying the Treatment of Injuries and Diseases of the Articulations, Lancet **2**:54, 1923.

determination that the nitrogen content in the mucin is equal to 13.26 per cent, they estimated the quantity of mucin by multiplying the nitrogen with 7.54. No evidence was given that the elementary analysis found in the effusions of normal cattle applies to the normal and especially to the pathologic effusions in human beings. The procedure therefore cannot be accurate. No determinations of phosphorus or sugar reaction were carried out. However, the authors made the valuable observation that the viscosity of three fluids after precipitation of the mucin dropped to the level found in plasma.

My review has shown that the mucinous substance was prepared in dry form and thoroughly investigated in only one effusion. This analysis disagreed with an older as well as with a later analysis of the normal synovial fluid in cattle in two important points: phosphorus content and sugar reaction. A reinvestigation was therefore indicated.

By separating the precipitate from the supernatant fluid by centrifugation instead of filtration, the whole process was carried out in one test tube. This had the further advantage that fat, lutein and cholesterol were separated as a scum on the top of the tube, thereby saving separate extraction and loss of material. With this modification enough dry substance for complete analysis can be obtained from 30 cc. of fluid.

The mucinous substance was prepared in dry form in eleven fluids of traumatic, of acute and chronic synovitis and of nonspecific, syphilitic and gonorrheal arthritis.

Method of Preparation of the Mucinous Substance.—Centrifugate the synovial fluid until it is perfectly clear. Make sure, under the microscope, that no cells are present. Transfer the clear synovial fluid to large centrifuge tubes with wide bottoms. Add slowly half the amount of 3 per cent acetic acid. Shake and centrifugate for ten minues. Remove the scum on the surface with a glass rod and decant the supernatant fluid. Fill to the original amount with 0.1 per cent sodium hydroxide. After dissolution, reprecipitate with half the amount of 3 per cent acetic and centrifugate. Decant the supernatant fluid, and wash the precipitate first with alcohol and then with water. Dry in a desiccator over sulphuric acid.

Traumatic effusions contain considerable bilirubin which is precipitated by the acetic acid. It is therefore necessary after the solution of the precipitate by the weak alkaline to add an equal volume of absolute alcohol and acidify by adding a few drops of glacial acetic acid and to centrifugate. The bilirubin is kept in solution by the alcohol. The supernatant fluid is yellow, and the precipitate turns whitish.

Properties of Mucinous Substance.—The mucinous substance is a yellowish or whitish amorphous substance with a waxen shine to the surface. It is translucent in thin plates, hard and nonflexible (fig. 5). It is soluble in diluted alkali, and the solution is sticky. It is insoluble in water, acids and alcohol. It can be precipitated by 3 per cent acetic acid, hydrochloric acid and alcohol. It does not contain phosphorus. Reduction of copper salts was negative. The reaction to the biuret test, modi-

fied according to my method,[24] was positive. Examination for purine bodies gave negative results. According to one estimation, it weighed 0.467 Gm. per hundred cubic centimeters of fluid.

Comment.—The reactions to acids and alkalines are typical for mucin. The absence of phosphorus and purine bodies excludes nucleoproteins (table 13). The sugar reactions were negative after prolonged hydrolyzation. Whether this is due to the absence of a nitrogenous sugar in the molecule or to some peculiarity, I am not prepared to state. Technical reasons prevented an elementary analysis, in which the determination of the sulphur content, especially, could throw light on the composition.

However, it is evident that the substance is not derived from disintegration of cartilage, as chondromucin readily reduces copper salts (table 12). The changes that take place in the fluid after precipitation reveal the significance of the mucinous substance.

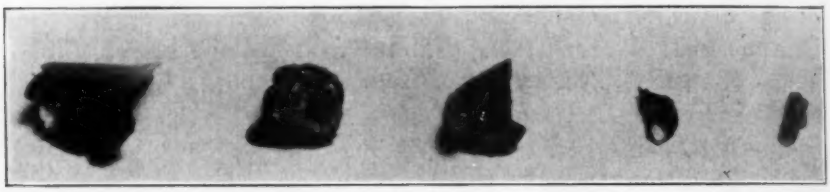

Fig. 5.—Several specimens of dry mucinous substance from synovial fluid.

The Supernatant Fluid.—The supernatant fluid is whitish or yellowish, the latter in traumatic effusions containing bilirubin. It is clear or, if the globulin content is high, somewhat turbid. The specific gravity is only slightly lower than it is in full fluid. The calculation shows this to be caused by the addition of the lighter acetic acid (table 14). This indicates that no marked changes in the protein content or salts have taken place by the removal of the mucinous substances. This is confirmed by the direct estimation of protein and globulins in one case (table 15). In two cases (table 16), the diffusible contents of blood, full and supernatant fluid are compared. If allowance is made for the limit of error, the differences are insignificant. The supernatant fluid still contains the bulk of colloids and diffusible constituents.

An enormous drop, however, occurred in viscosity equal to a decrease between 312 and 1,780 per cent (table 17). The range of variation between the minimum of 0.8 and the maximum of 1.09 is well within the limits of viscosity for transudates and exudates. The peculiar

24. Kling, D. H.: A Convenient Modification of the Biuret Test, J. Lab. & Clin. Med. **15**:185, 1929.

precipitation phenomena disappeared. The fluid no longer showed sack formation but gave either a positive or a negative Rivalta reaction. In short, the supernatant fluid has all the physical and chemical characteristics of simple transudates or exudates.

TABLE 16.—*Chemical Analysis of the Blood and of Full and Supernatant Synovial Fluids in a Fasting Patient, Expressed in Milligrams per Hundred Cubic Centimeters*

Fluid	Sugar	Urea Nitrogen	Creatinine	Chlorides	Calcium*	Phosphorus*
Blood	82	11.3	1.77	477	10.1	3.12
Synovial	94	12.1	1.50	502	7.8	2.96
Supernatant	94	13.1	1.39	600	8.8	2.84

* Estimated on a second fasting patient.

TABLE 17.—*Specific Viscosity of Synovial Fluid Determined in Full, Supernatant and Globulin-Free Specimens*

	Specific Viscosity				
No.	Full	Supernatant (Mucin-Free)	Decrease, per Cent	Globulin-Free	Decrease, per Cent
1	16.8	1.6	1.050	10.0	40.5
2	16.0	0.9	1.718	9.6	40.0
3	16.0	0.9	1.718	9.2	42.5
4	32.0	1.9	1.780	28.2	11.8
5	13.6	1.9	0.720	9.2	32.3
6	13.4	1.4	0.960	9.2	31.3
7	2.5	0.8	0.312	1.6	36.0
8	28.0	1.8	1.550	....	....
9	16.8	1.6	1.050	....	....
10	16.0	1.6	1.000	....	....
11	11.4	1.7	0.670	....	....
12	12.0	1.3	0.920	....	....
13	14.8	1.2	1.230	....	....

TABLE 18.—*The Composition of Synovial Fluids*

Origin	Synovial Membrane	Circulation
Supplies	Mucinous substance	Plasma
	Synovial cells	Blood cells
Properties	Protection, lubrication	Nutrition
	Antibodies	Antibodies

Composition of Special Types

Type	Source	Cells	Percentage*
Normal fluid	Synovial membrane	Tissue	
Transudates	Circulation	None	2
Exudates	Circulation	Blood	4
Inflammatory and traumatic effusions	Circulation and synovial membrane	Blood and synovial cells	94

* Calculated on the basis of 200 pathologic effusions.

A direct proof that the mucinous substance produces both the precipitation reactions and the increase in viscosity is given in the following experiment. About 5 mg. of the dry substance was dissolved in 10 cc. of serum to which a drop of 10 per cent sodium hydroxide was added. The viscosity of the serum was raised from 1.7 to 4, and sack formation appeared. Previously even the Rivalta reaction had been negative.

THE ORIGIN OF NORMAL AND PATHOLOGIC SYNOVIAL FLUIDS

This investigation revealed a dual composition of pathologic effusions. The supernatant fluid after precipitation with acetic acid contains proteins and diffusible constituents of plasma, transudates and exudates. Their distribution indicates that they are derived from the circulation by diffusion (Fremont-Smith). They represent the systemic response to inflammation. In traumatic effusions they are carried into the joint cavity by the rupture of a vessel. The mucin-like precipitate, however, is not present in the plasma. It is produced by the synovial membrane. It is demonstrated in the fluids of normal joints as well, and must therefore be regarded as a physiologic product. Inflammation and irritation only tend to increase its output. This substance determines the physicochemical properties of synovial fluid, like stickiness, sack formation, viscosity and precipitation. Its biologic function is entirely different from the fraction derived from the circulation. The proteins and crystalloids of the latter are a source of energy and nutrition. The mucinous substance is adopted for protection and lubrication of the articular surfaces.

This is a foremost requirement of the working, healthy joint. Normal synovial fluid consists, therefore, of a small amount of this colloidal lubricant furnished by the membrane according to the requirement for proper function. The fine adjustment that characterizes living matter is well demonstrated in the synovial fluid.

The slightest disturbances, like the absence of motion (Frerichs and Horyi), are of influence. Irritation and inflammation produce changes in the amount and composition of synovial fluid proportional to the degree of disturbance. This applies to the cellular elements as well as to the liquid portion.

Normal synovial fluid contains few cells, and they are chiefly synovial lining cells.[25] Different types of leukocytes in various amounts, according to the stage and the degree of the process, are found in inflammatory effusions; trauma brings red blood corpuscles into the fluid.

The Mechanism and the Place of the Elaboration of Normal Synovial Fluid.—Changes in anatomic conceptions of the synovial membrane resulted in different theories regarding the source of synovial fluid. Some still propose that it is a product of disintegration either from the superficial cells of the synovia (Frerichs) or from cartilage (Ogston[26] and Bianchi[27]). This is based on an erroneous analogy to the horny layers of epidermis.

25. Kling, D. H.: Synovial Cells in Joint Effusions, J. Bone & Joint Surg. **12**:867, 1930.

26. Ogston, quoted by Fisher (footnote **23**).

27. Bianchi, quoted by Mayeda (footnote 13).

The superficial lining cells of the synovia are seen to be intact in fresh preparations; their nuclei and cytoplasm stain well. Also the superficial cells of the articular cartilage appear healthy; they are nearest to the perichondrium in the lateral parts of the cartilage. Fisher advances the theory that the superficial cells generate the deeper layers in the central portion.

Benninghoff [28] demonstrated that their fibers form an important system in the architectonic structure of the articular cartilage. The clean appearance of the normal joint cavity and the small amount of débris in the contents also disprove this antiquated theory.

The conception of the synovial membrane as a modified connective tissue, not endowed with secretory elements, advanced the theory that the synovial fluid is a transudate. The analysis has demonstrated that this applies only to one fraction of the pathologic effusions. The physicochemical properties and the function indicate that the normal synovial fluid is a product of specialized cell activity.

The anatomic basis for this view was furnished by an extensive histologic study by Mayeda. The synovial membrane is not of uniform structure. In 1894, Hammer noticed the great variation in the forms and the number of the lining cells. Key [29] recently emphasized the variation in the subsynovial tissue.

Mayeda proved that the function of different parts varies with the structure. The distal part of the suprapatellar bursa and the membrane of the posterior aspect of the knee joint are composed of a firm connective tissue and covered by a single and partly interrupted row of small, flat cells. The plica adiposa, the fornix of the suprapatellar pouch and the villi contain loose subsynovial tissue and several rows of large polygonal cells. By special staining methods, Mayeda demonstrated in some of these cells Altmann granules, Haidenhain granules and also mucin granules. These gave a positive oxydase reaction, and accumulated and excreted colloidal iron solutions, injected intravenously. The secretory nature of the cells producing the mucinous substance was therefore proved.

Timbrell Fisher in a later publication observed mucin in cells of the villi, stained with thionine. In preparations fixed with sublimate and stained with toluidine blue, I have demonstrated in sections and in scrapings the presence of cells with metachromatic reddish or purple granules that filled the cytoplasm. The nuclei were normally shaped and well stained, and were therefore not degenerated.

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28. Benninghoff, A.: Die modellierenden und form-erhaltenden Faktoren der Knorpelreliefs, Ztschr. f. d. ges. Anat. **76**:43, 1925.

29. Key, Albert: Synovial Membrane in Special Cytology, New York, Paul B. Hoeber, Inc., 1928, vol. 2.

In summary it can be said that the structure and the function of the synovial membrane are twofold. One part is built for mechanical binding of the epiphyses constituting the joint; it is connective tissue capsule, inward and outward. The other part is interposed at the intratesticular surfaces, for the maintenance of smooth motion and lubrication. This is the function of the intra-articular fat depots, synovial folds and villi and their lining containing actively secreting cells.

The conception of the composition of the synovial fluid on the basis of these studies is summarized in table 18. Normal fluid is chiefly secreted by the synovial membrane. Transudates and exudates forming 6 per cent of a series of 200 fluids are derived from the circulation. Ninety-four per cent of the traumatic and inflammatory effusions contained products of both circulation and synovial secretion.

CLINICAL CONSIDERATIONS

The clinical significance of the differentiation of the structure of the membrane and of the normal and pathologic synovial fluids is a subject for separate study. Here I shall point out briefly some of the applications.

The Protective Influence of Synovial Secretion.—The development of the membrane and of the fluid is different in various joints. The secretory element is best developed in the knee joint and less well developed in the wrist and tarsal joints. The primary response to inflammation and irritation of the knee is therefore effusion; that of the wrist, infiltration and pannus formation. This explains why the same etiologic factor, for instance gonorrhea, produces in the same patient a chronic exudative arthritis of the knee joint and an infiltrative and ankylosing process of the wrist.

Motion is the natural stimulus for the secretion of synovia, as is food for the secretion of gastric juices. The detrimental effect of immobilization, especially in knee joints, is therefore explained by the interference with this secretion in a joint highly adapted to it.

The protective action of the synovial secretion is further seen by the fact that forms of arthritis with effusions generally have a better prognosis than the infiltrative, atrophic forms. In the latter the synovial membrane undergoes early destruction, and the process spreads over the cartilaginous and bony surface without a barrier. The atrophy reaches a high degree and ankylosis occurs. In arthritis with effusions, inflammation is met with hypertrophy and hypersecretion of the membrane, the articular surfaces are protected, and the resulting atrophy is only proportional to the decrease in function.

The Relation Between Trauma and Inflammation.—Physiochemical analysis has demonstrated the almost immediate reaction of the synovial

membrane to intra-articular injuries. Of the seventy-eight cases of acute hemorrhagic effusion, only two contained blood corpuscles and serum alone. The hemorrhagic fluid in all others had a high viscosity, sack formation occurred, and the mucinous body was precipitated by acetic acid, even in the first days after injury. Besides the mechanical disturbance, the hemarthrosis therefore produces an irritation and hypersecretion. Although self-limited by absorption in the majority of injuries, in some cases the process continues. This explains the frequent transition of traumatic effusion into chronic synovitis and the development of diminished resistance in injured joints. In many cases of monarticular arthritis, careful inquiry reveals a trauma preceding by months and even years an inflammatory process, which may have been brought about by influenza, tuberculosis, syphilis or gonorrhea.

Osteochronditis Dissecans and Loose Bodies.—Osteochondritis dissecans and loose bodies offer a good opportunity to demonstrate the difference in function of the two components of synovial effusions. The pathologic process in osteochondritis dissecans consists of the necrosis of a shell of the articular cartilage. If Strangeways'[30] and Fisher's contentions that normal synovial fluid has a nutritive value are true, how could the necrosis ever have taken place? Even if the shell were cut off from the circulation, it could find nourishment in the synovial fluid. This is not the case as long as the necrotic piece of cartilage is still attached. In my cases, I had the opportunity to observe at operation that no irritation of the synovial membrane was present; the synovial fluid was normal in amount and composition. As soon, however, as the fragment of cartilage becomes detached and free it impinges on different parts of the membrane during motion and produces irritation and transudation from the vessels, which import the proteins and sugar needed for nutrition by diffusion.

The cartilage cells start to generate and the loose bodies grow. Unlike necrosis without detachment, effusion is usually associated with loose bodies. They grow, therefore, because they produce their pabulum and not because it is already formed.

SUMMARY

Studies on the source and origin of synovial fluid were carried out on a material of thirteen normal fluids and two hundred pathologic effusions.

Normal fluids and about 95 per cent of the effusions gave precipitation phenomena with diluted acetic and hydrochloric acid, consisting of

30. Strangeways, T. S. P.: The Nutrition of Articular Cartilage, Brit. M. J. **1**:661, 1920.

membranes and sacks. Analogous phenomena were found with mercuric chloride solution, and somewhat modified phenomena with alcohol.

These reactions were not found in plasma transudates and exudates from other cavities of the body; they were, however, demonstrated in fluids that were cell secretions, like saliva and egg white.

The viscosity of normal, and the majority of pathologic, synovial fluids is higher and the range of variation is greater than that found in plasma and exudates.

The specific gravity, on the other hand, is in the range of that for body fluids.

Accordingly, the substances that determine the specific gravity, the proteins and crystalloids and their fractions, were found to be in the range of these fluids.

It was experimentally proved that none of the colloids and diffusible constituents of plasma produce a difference in viscosity and formation of sacks. The blood gases and the p_H were demonstrated to be without marked influence.

A mucinous substance was prepared in dry form from the effusions of the joints, which was proved to be responsible for the physicochemical properties of synovial fluids.

Mucin granules were demonstrated by special staining reactions in active cells in well defined areas of the synovial membrane, confirming the earlier work of Mayeda and of Fisher.

The mucinous substance is recognized to be a physiologic product.

Motion is the adequate stimulus, and lubrication and protection are the functions, of this secretion.

Normal synovial fluid is finely adjusted to the physiologic requirements.

Mechanical or inflammatory disturbance of the structure and function of the joint causes changes in the amount and composition of this secretion.

Ninety-four per cent of the pathologic effusions in this material were derived from both cell secretion and circulatory extravasation.

Four per cent are considered to be pure exudates or transudates.

On the basis of the physiochemical and anatomic studies, the view is advanced that the structure and function of the synovial membrane are twofold: a connective capsule for binding purposes in which secretory elements are interposed.

The clinical applications of these studies are illustrated in a number of pathologic conditions.

The material for these studies was derived from the orthopedic services of Drs. Harry Finkelstein, Henry C. Frauenthal, Samuel Kleinberg and Leo Mayer of the Hospital for Joint Diseases.

THE UNION OF GRAFTS OF LIVE AND OF PRESERVED FASCIA WITH MUSCLE

A COMPARATIVE STUDY *

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The study of the union of normal fascia with muscle has been the subject of a number of investigations. Because of the close relationship of this problem to the one to be presented it seems advisable to review some of these papers briefly.

In a report based on experimental and clinical observations, Seelig and Chouke [1] stated that muscle would not unite with fascia. They performed a series of experiments on animals, in which they reduplicated the fascia lata to simulate Poupart's ligament, and sutured the edge of the turned flap to the underlying muscle. In every experiment they found that the fascia lata was separated from the muscle by loose areolar tissue and failed to unite firmly. Koontz [2] repeated the experiment of Seelig and Chouke, but removed the loose areolar tissue from the fascia lata; he obtained firm union in every case. He claimed that the failure of the other investigators was due to the fact that they did not remove the fat. Seelig and Chouke [3] each independently repeated their experiments, removing the adipose tissue, and again found that the fascia failed to unite. Rosenblatt and Cooksey,[4] in a similar series of experiments, obtained union in every instance. Hertzler [5] thought that the discrepancies in the results of the various investigators was due to the fact that Seelig and Chouke tied their sutures loosely and thus did not produce the traumatic reaction that is fundamental in obtaining a firm union. The other investigators tied their sutures tightly, and so caused the fibrous stimulation that is necessary for union in the presence of fat.

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* Submitted for publication, Jan. 27, 1931.

* From the Surgical Laboratory, Stanford Medical School.

1. Seelig, M. G., and Chouke, K. S.: A Fundamental Factor in the Recurrence of Inguinal Hernia, Arch. Surg. **7**:553 (Nov.) 1923.

2. Koontz, A. R.: Muscle and Fascia Suture with Relation to Hernia Repair, Surg. Gynec. & Obst. **42**:222 (Feb.) 1926.

3. Seelig, M. G., and Chouke, K. S.: Fundamental Principles Underlying the Operative Cure of Inguinal Hernia, J. A. M. A. **88**:529 (Feb. 19) 1927.

4. Rosenblatt, M. S., and Cooksey, W. B.: Muscle Fascia Suture in Hernia, Ann. Surg. **86**:71, 1927.

5. Hertzler, A.: Healing of Muscle to Fibrous Tissue, J. A. M. A. **88**:1098 (April 2) 1927.

The preponderance of evidence from all of these studies favors the view that muscle will unite with fascia.

The next problem to present itself was whether or not a transplant of free fascia would unite with muscle. Some surgeons, particularly Lange, have held that transplanted fascia would not unite firmly with muscle fibers. These assertions were made in spite of the fact that Payr, in 1913, had successfully used transplanted fascia lata for the union of the cut end of the trapezius muscle to the tendon of the long heads of the biceps. Gallie [6] likewise used a transplant of free fascia interwoven into the trapezius muscle and then united it to the humerus to replace a paralyzed deltoid. Mayer's [7] operation, based on a principle similar to that of Gallie, but with a somewhat different mechanical arrangement, also depends on the union of transplanted fascia to muscle.

In addition to the successful clinical results just reported, I performed a series of experiments [8] in order to determine the details of the union of live fascia with muscle. As the results of these experiments are to be compared with those of the present investigations, a review of that paper will be helpful in formulating the conclusions of the two.

The study consisted of six experiments performed on dogs in which a piece of fascia lata was removed from the outer side of the thigh and sutured to the cut end of one of the hamstring muscles with silk. As early as sixteen days after the operation, the transplanted fascia was found to be firmly united to the cut end of the muscle. The union became firmer with the lapse of time, and at eighty days the transplanted fascia took on a tendinous structure. Microscopic examination showed that the endomysium and perimysium of the muscle played the major rôle in forming the union with the fascia. The muscle cells appeared to have taken an active part in the uniting process. The muscle cells became transformed into elements of fibrous tissue which intermingled with the transplanted fascia. There was also evidence that the connective tissue fibers of transplanted fascia took an active part in the union.

These experimental observations and the clinical results established the fact that live, transplanted fascia will unite with muscle. No exact experimental work or clinical results have thus far been presented to show whether dead transplanted fascia will unite with muscle. If fascia

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6. Gallie, W. E., and Le Mesurier, A. B.: The Use of Living Sutures in Operative Surgery, Canad. M. A. J. **11**:504, 1921.

7. Mayer, L.: Transplantation of the Trapezius for Paralysis of the Abductors of the Arm, J. Bone & Joint Surg. **9**:412 (July) 1927.

8. Haas, S. L.: Free Fascial Grafts; Their Union with Muscle, California & West. Med. **32**:387 (June) 1930.

is an inert tissue, as claimed by Nageotte,[9] one would infer that dead tissue could be utilized just as successfully as live tissue for purposes of transplantation. On the other hand, if the cellular elements of transplanted live fascia play an active part in the union, and there is evidence that they do, it may be advantageous to utilize live tissue instead of preserved fascia. Furthermore, the chemical fixation of the tissue may hinder the union.

Koontz[10] used preserved fascia for suture material in the repair of hernia. Although his experiments are not exactly comparable to the union of muscle and preserved fascia, they are of sufficient interest to warrant reporting at this time. He found that if fascia that had been preserved in alcohol, was transplanted into a defect in living fascia, it intermingled so closely with the live tissue that it was almost impossible to distinguish the dead from the living part. Heterografts were just as successful as homografts. Following the method of Gallie and Le Mesurier, Koontz then successfully utilized sutures of preserved fascia lata from the ox to unite the tissues in hernia in man. Rosenblatt and Meyers[11] performed a series of experiments in which they sutured the edge of the rectus muscle to Poupart's ligament with preserved ox fascia and tendon sutures. In studying the completely healed line of surture, they found that the preserved fascia sutures were smaller than they had been when they were inserted, and that there was some evidence of foreign body reaction. Koontz and Nageotte did not report the presence of foreign body giant cells or evidence of absorption in their experiments.

The direct union of a preserved piece of fascia with muscle presents a more complicated problem than the utilization of fascia for suture material. In the following set of experiments the problem is directly attacked and it is hoped that some light may be thrown on this interesting subject.

REPORT OF EXPERIMENTS

Seven experiments were performed on dogs under general ether anesthesia. The fascia lata was obtained prior to the operation and preserved in alcohol. At the time of the operation it was washed in sterile water. It was thought that the staining of the tissue with methylene blue (methylthionine chloride, U. S. P.) or gentian violet would tend to differentiate it on gross examination, but the stain disappeared by the time the animal was killed. In all of the experiments an incision was made on the inner posterior side of the hind leg, one of the hamstring muscles being exposed. A piece of tendon and muscle was removed and a seg-

9. Nageotte, J., and Sencert, L., quoted by Koontz, A. R.: Ann. Surg. **83**: 523, 1926.

10. Koontz, A. R.: Experimental Results in the Use of Dead Fascia Grafts for Hernia Repair, Ann. Surg. **83**:523, 1926.

11. Rosenblatt, M. S., and Meyers, M.: Muscle-Fascia Suture with Preserved Fascia and Tendon, Surg. Gynec. & Obst. **47**:836, 1928.

ment of preserved fascia sutured into the defect. At the end of the period of observation the animals were killed by an anesthetic, and the specimen was removed and studied grossly and microscopically.

EXPERIMENT 1 (dog DT3).—An incision was made on the inner side of the left leg just above the knee joint, exposing the semimembranosus muscle. A section of the muscle, including a part of the tendon, was removed and a piece of the preserved fascia lata was sutured into the gap with silk sutures. The wound was closed in layers, and the animal allowed its freedom.

When the dog was killed at the end of twenty-two days, the transplanted fascia was found to have firmly united to both the muscle and the tendon (fig. 1). The fascia was a mottled yellowish white, differing from the uniform grayish white of the live, transplanted fascia.

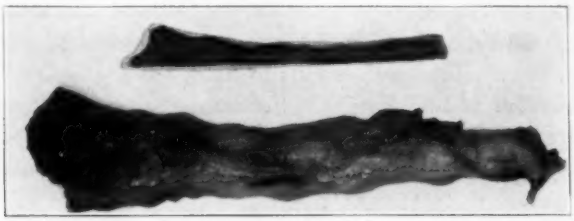

Fig. 1 (experiment 1).—Gross appearance of the union of dead fascia with muscle. The smaller photograph is a longitudinal section through the fixed specimen. It shows the close intermingling of the muscle and the fascia.

Fig. 2 (experiment 2).—Gross appearance of the union of dead fascia with muscle.

Microscopic examination showed that there was a close intermingling of muscle and fascia at the site of union. The endolysium (fascia uniting the individual muscle cells) and the perimysium (fascia uniting the bundle of muscle cells) were the most active elements in the uniting process. At the end of the muscle cells there were clumps of nuclei which were not giant cells but which appeared to be formed by an active proliferation of endomysium and nuclei of the muscle cells. Some of the nuclei were undergoing indirect division. The fibrillae of the muscle cells were breaking down and appeared to be engaging in the process of union. One could not distinguish between the dead, preserved tissue and the live tissue. It is to be remembered that the preserved tissue had been fixed in alcohol, and that which had not been replaced by ingrowing tissue had, owing to its fixation, retained the property of taking the usual stains.

EXPERIMENT 2 (Dog DT3).—The semimembranosus muscle was exposed on the right side and a piece excised from the muscle at its transition into the tendinous portion. A segment of preserved fascia was sutured into the gap.

Gross examination after thirty-eight days showed that the preserved fascia that had been stained in gentian violet before its implantation was completely decolorized (fig. 2). The union was firm, but the healing was not so uniform as when a live piece of fascia was utilized. Microscopic examination revealed a gradual transition from the muscle to the transplant of preserved fascia. The elements

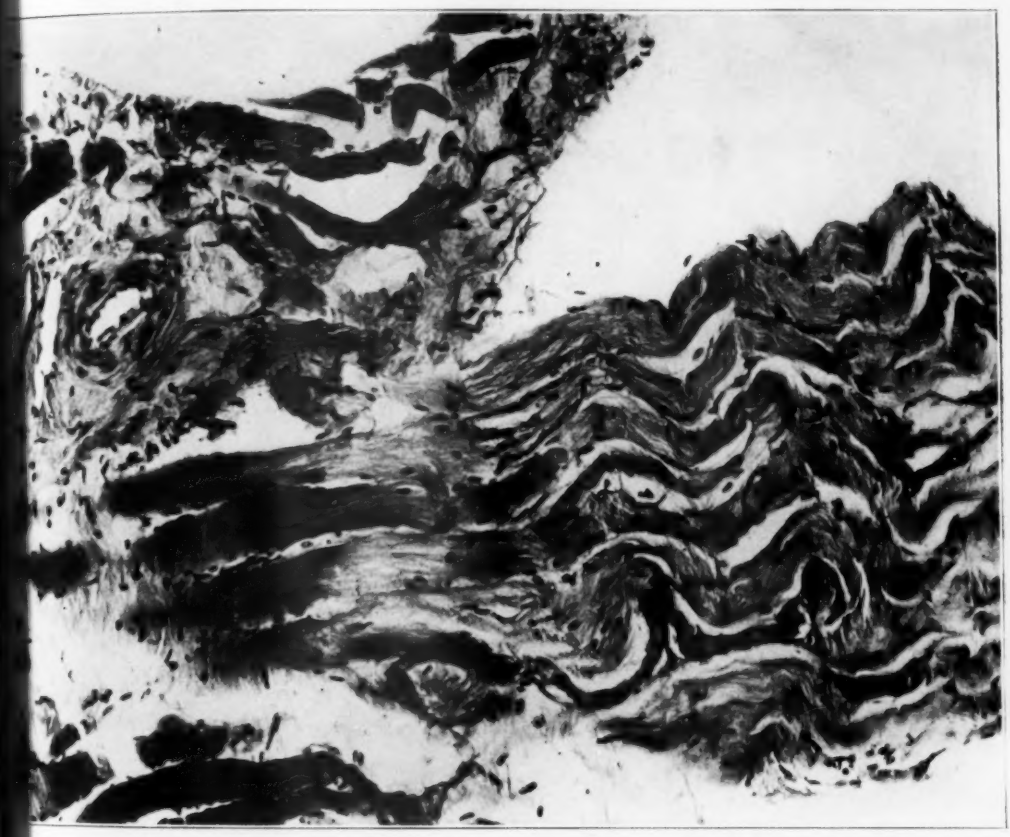

Fig. 3 (experiment 2).—Photomicrograph showing the breaking down of the muscle cells. The fibrillae of these cells take on a wavy, fibrous, tissue-like structure and invade the transplanted preserved fascia.

of muscle were undergoing fragmentation. The fibrillae of the muscle cells had taken on a wavy structure (fig. 3) and gradually merged into the fibrous tissue structure of the transplanted fascia, no line of demarcation being made out. The transplanted fascia was more cellular than normal, which must have been due to additional, new elements of invading tissue from the muscle.

EXPERIMENT 3 (Dog DT3).—The semimembranosus muscle on the left was exposed, and a segment of muscle and tendon removed at the junction of the

muscle with the tendon. A piece of preserved fascia was sutured to the muscle in such a manner that the fascia was within the outer layers of muscle.

After forty-two days, examination of the gross specimen showed that the fascia was firmly united to the muscle. Its consistency was fairly firm, but it appeared to have lost some of its elasticity. The union with the tendon was likewise quite firm. Microscopic examination revealed that the process of union was more advanced than had been found in the earlier stages. The two tissues graded off so uniformly that there was no line of demarcation to distinguish the site of union (fig. 4).

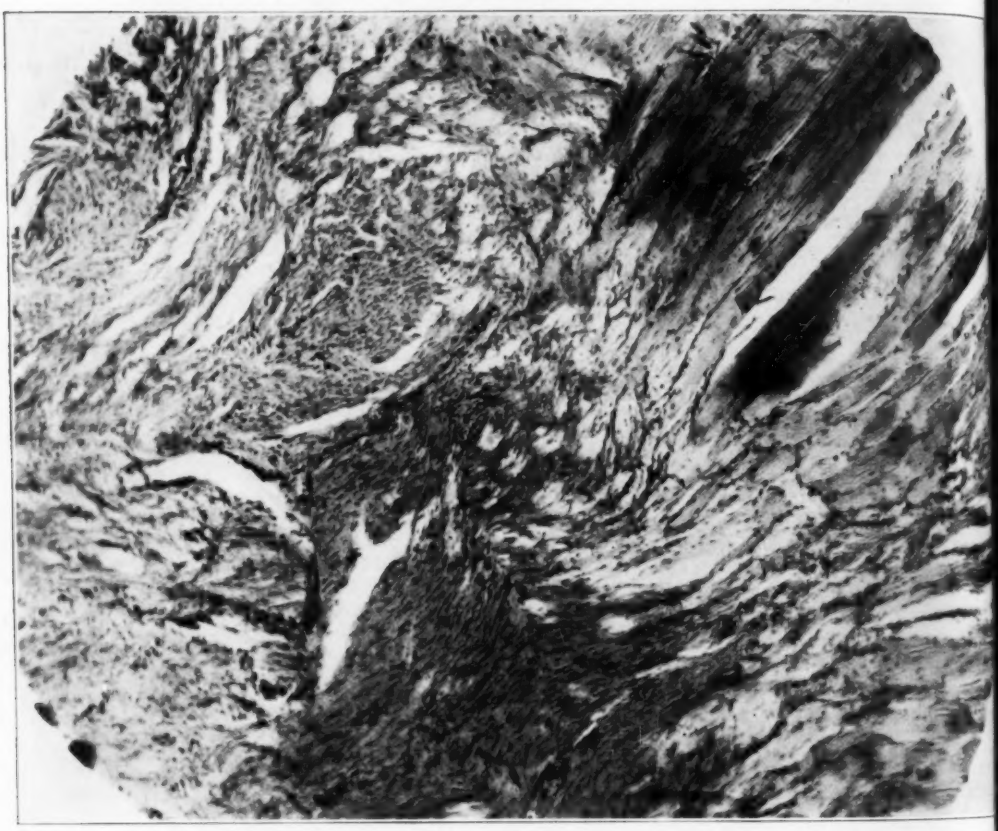

Fig. 4 (experiment 3).—Photomicrograph of the union of preserved fascia with muscle. This shows the close intermingling of the two tissues formed by the endomysium, perimysium and muscle cells.

EXPERIMENT 4 (Dog DT4).—The semimembranosus muscle was exposed on the left, and a piece removed at the place where the muscle passed into the tendon. A segment of preserved fascia lata was sutured into this defect with interrupted silk sutures.

In spite of an infection that had taken place, examination of the gross specimen after forty-two days showed that there was firm union between the fascia and the

muscle. The transplanted fascia and surrounding tissues appeared edematous. Microscopic examination showed a definite union between the muscle and fascia. The endomysium and perimysium were invading the transplanted fascia. The muscle cells themselves appeared to be taking part in the union.

EXPERIMENT 5 (Dog DT1).—The semimembranosus muscle was exposed on the left side by an incision on the inner side of the leg above the knee joint. A section of muscle and tendon was excised where the muscle passed into the tendon. Into this gap a piece of preserved fascia lata was sutured so that the fascia extended around the cut end of the muscle.

After forty-three days, examination of the gross specimen showed that there was firm union between the muscle and the transplanted fascia. The fascia itself was firm and had taken on a tendinous structure. The union between fascia and tendon was also firm. Microscopic examination under low power magnification showed the junction of the muscle with the fascia. There was a lighter staining fibrous tissue near the muscle that merged into a darker, red-staining tissue. The lighter tissue probably represented the new fibrous tisssue that formed the union of the two, while the darker staining tissue represented the dead (fixed) fascia that had not been changed. Under higher magnification, a proliferation of fibrous tissue from the muscle side could be seen. Undoubtedly, the greater part of this proliferation was from the perimysium and endomysium. A close study of the muscle cells showed what appeared to be a breaking up of the fibrillae and their change into fibrous tissue-like elements. In places there was a proliferation of the nuclei about the ends of the muscle, forming budlike masses. Thus it appears that union takes place through a proliferation of the perimysium and endomysium and to a lesser degree through the breaking down of muscle cells. That there may be an ingrowth of fibrous tissue from the outside cannot be ruled out, but one gets the impression from the general longitudinal architecture and lack of invading tissue that the elements of muscle alone are concerned in the union.

EXPERIMENT 6 (Dog DT1).—Through an incision on the inner side of the right leg just above the knee joint, the semimembranosus muscle was exposed, and a segment of muscle and tendon was removed at their junction. A piece of preserved fascia lata was inserted into the gap and held with interrupted silk sutures.

The dog was killed after sixty-three days, and examination of a gross specimen showed that the transplanted fascia was firmly united to the muscle. The whole transplant was gelatinous and edematous, and lacked the firm consistency found when live transplanted fascia was utilized. Microscopic examination showed a direct union of the muscle with the fascia. The cellular response did not appear to be as active as in the earlier stages. This may have been due to the fact that there was less demand in this particular case because of the close approximation of the two. The fibrillae of the muscle cells appeared to be breaking down, and there was an increase in the number of nuclei at their ends. Both the sarcolemma and the endomysium showed evidence of cellular activity.

EXPERIMENT 7 (Dog DT4).—An incision was made on the inner posterior side of the right knee joint, one of the hamstring muscles being exposed. A section of muscle was removed and a piece of preserved fascia lata sutured into the gap with interrupted silk sutures.

The animal was killed after sixty-three days, and examination of the gross specimen showed that the preserved fascia had united firmly to the muscle. In this experiment, the fascia had been placed in a gap in the muscle, the distal portion of which had degenerated and was replaced by fibrous tissue. Microscopic

examination showed that the muscle and preserved fascia were closely united. The endomysium and the perimysium supplied the greater part of the connective tissue to the union. The muscle cells appeared to be transforming into elements of fibrous tissue and sharing in the union.

SUMMARY

In all of the seven experiments, the transplanted, preserved fascia united firmly with the muscle. At the end of twenty-two days, which was the earliest observation, union was almost secure. With the elapse of further time the union was more complete. The transformed tissue did not tend to take a firm, tendinous structure, but in general was somewhat gelatinous (edematous). Pathologic examination showed a close intermingling of the muscle and the transplanted fascia. The endomysium and the perimysium played the major rôle in the union. The muscle cells showed definite evidence of proliferation and of having aided in the uniting process. There was no evidence of foreign body reaction or absorption, and the collection of nuclei in groups was interpreted as proliferating cells.

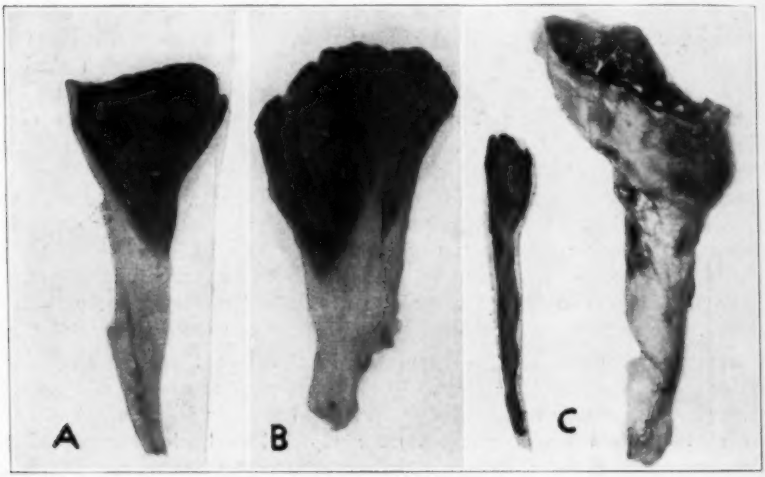

Fig. 5.—(*A*) Specimen showing the junction of normal muscle with tendon. (*B*) Section through the union of transplanted fascia with muscle. (*C*) Section through transplanted, preserved fascia with muscle.

Comparison of Live and Preserved Fascia.—The union of the preserved fascia lata with the muscle apparently took place as rapidly as that with live fascia. The preserved fascia lata looked more edematous and appeared to be less compatible to the surrounding tissues (fig. 5). The live fascia was more tendinous and retained more of its elasticity.

On microscopic examination, there was no apparent difference between the union of dead fascia with muscle and that of live fascia (fig. 6). The same elements took part in the union, the greater amount coming from the endomysium and the perimysium, and there was the same evidence that the muscle cells shared in the process. Although grossly there was some sign of foreign body reaction when dead fascia was employed, no foreign giant body cells or evidence of absorption were

Fig. 6.—Photomicrograph of the junction of muscle with live, transplanted fascia. Notice the similar histologic picture to that found in the union of transplanted, preserved fascia with muscle in figure 4.

found in the dead fascia. One could not say whether the dead fascia survived permanently or was replaced by ingrowing tissue from the muscle, or that both shared in the process.

CONCLUSION

Dead, preserved fascia lata united with muscle just as rapidly and as firmly as did live fascia lata. The union of both dead and live

fascia depended mainly on the ingrowth of the endomysium and perimysium. The muscle cells themselves appeared to be transformed into elements of fibrous tissue and to aid in the uniting process. There was some evidence that the preserved fascia lost some of its elasticity and stirred up more reaction in the surrounding tissue than did live fascia. Dead, preserved fascia may be used clinically for union with a muscle, but it seems advisable to utilize the live fascia if possible, because the latter appears to be transformed into tendinous tissue more readily.

SKELETAL METASTASES ARISING FROM CARCINOMA AND FROM SARCOMA*

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Advances in the diagnosis and treatment of a disease entity are dependent on a knowledge of all the available data both from a clinical and from a pathologic point of view and from the results obtained by the various modes of therapy.

In the following study, an attempt will be made to correlate the various clinical features with the pathologic process involved, and to throw some light on the rather obscure results that have hitherto obtained in the treatment for metastases of the bone.

For purposes of analysis, it has been found convenient to group the 334 cases of bony metastases according to the primary tumor from which the dissemination occurred, thus emphasizing the entire clinical picture of each type of secondary neoplastic deposit, and, so far as possible, to determine accurately the process of histogenesis and the variations in response to treatment.

CARCINOMA OF THE BREAST

Carcinoma of the breast constitutes one of the most frequent primary tumors metastasizing to bone.[1] A survey of 1,914 cases of mammary carcinoma in the Surgical Pathological Laboratory of the Johns Hopkins Hospital revealed 903 deaths, 757 of which were caused by dissemination of cancer and 146 from causes other than malignant disease. In 89 (11.8 per cent) cases in which death was due to cancer, lesions of the bone were found prior to death. In addition to these fatal cases, 12 other patients, not yet reported dead, have developed metastatic

* Submitted for publication, Sept. 29, 1930.

* Illustrations by Herman Schapiro.

* From the Department of Surgery and the Surgical Pathological Laboratory of the Johns Hopkins Hospital and University.

1. Joll, C. A.: Metastatic Tumors of Bone, Brit. J. Surg. **11**:38, 1923-1924. Moore, A. B.: A Roentgenological Study of Metastatic Malignancy of the Bones, Am. J. Roentgenol. **6**:589 (Dec.) 1919. Carnett, J. B., and Howell, J. C.: Bone Metastases in Cancer of the Breast, Ann. Surg. **91**:811 (June) 1930. Handley, W. S.: Cancer of the Breast and Its Operative Treatment, London, John Murray, 1906, pp. 1-176. Kaufmann, E.: Sekundäre Geschwülste der Knochen, Spezielle pathologische Anatomie **1**:954, 1922. Gross, S. W.: Skeletal Metastases in Carcinoma of the Breast, Am. J. M. Sc. **95**:219, 1888. Ginsburg, S.: Pain in Cancer of the Breast: Its Clinical Significance with Special Reference to Bone Metastases, ibid. **171**:520, 1926.

TABLE 1.—*Cases of Carcinoma of the Breast with Metastases to Bone*

Path. No.	Color	Sex	Age	Primary Tumor	Location of Primary Tumor	Primary Operation	Location of Metastases	Pathologic Fracture	Interval Between Appearance of Tumor and Metastases	Interval Between Primary Operation and Metastases	Treatment of Metastases	Duration of Life Following Metastases
44695	W	F	40	Cystic adenoma, carcinoma	Right breast	Gland biopsy, right axilla	5th, 6th and 7th thoracic vertebrae	.....	27 months	3 months	Radium, 6 Gm. hrs.	Lost
44643	W	F	36	Adenocarcinoma	Left breast	Radical amputation	Spine, ribs	.....	33 months	9 months	.....	Lost
42840	W	F	..	Adenocarcinoma	Left breast	Radical amputation	Ribs, pelvis, upper end of femur	.....	.....	1st op.: 42 mo. 2d op.: 21 mo.	.....	Living after 1 mo.
				Scirrhous carcinoma	Right breast	Amputation of breast						
42718	W	F	..	Scirrhous carcinoma	..... breast	Excision of tumor	Pelvis	.....	.....	.....	.....	.....
41294	W	F	45	Carcinoma	Left breast	Radical amputation	Lower part of lumbar spine, pelvis and hip joints	.....	60 months	34 months	X-rays	Living after 18 mo.
41234	W	F	..	Carcinoma	..... breast	Radical amputation	Humerus, clavicle, pelvis	.....	33 months	20 months	.....	Living 24 mo., 1928
40830	W	F	63	Scirrhous carcinoma	Left breast	Radical amputation	4th and 5th lumbar vertebrae, pelvis, sacrum, upper part of femora	.....	72 months	.....	X-rays	Living 9 mo.
40716	W	F	45	Scirrhous carcinoma	Right breast	Radical amputation	3d and 4th lumbar vertebrae, right ilium, right sacroiliac joint	.....	.....	12 months	X-rays (24 times)	Living 12 mo., 1928
40585	W	F	70	Medullary carcinoma	Right breast	Radical amputation	Bone (right leg)	.....	.....	.....	.....	Dead
40536	W	F	62	Scirrhous carcinoma	Left breast	None	Upper end of left femur, lower third of right femur, upper end of right femur	.....	4 months	.....	X-rays	Lived 2 mo., 4 wk.
40368	W	F	47	Scirrhous carcinoma	Right breast	Radical amputation	Skeleton	.....	.....	.....	.....	.....
40002	W	F	42	Scirrhous carcinoma	Right breast	Radical amputation	Upper end of right femur, ilium	Femur below trochanter	2 weeks	.....	Resection head, neck, right femur; x-rays	Lived 12 mo.
39788	W	F	39	Cystic adenoma, carcinoma	Left breast	Amputation of breast	Spine	.....	.....	.....	.....	Dead
38936	W	F	47	Scirrhous carcinoma	Right breast	Radical amputation	2d lumbar vertebra	.....	20 months	19½ months	X-rays	Living 10 mo., July, 1929

38850	W	F	36	Scirrhous carcinoma	Right breast	Radical amputation	Spine	.....	.....	.....	.....	.....
38805	W	F	70	Scirrhous carcinoma	Left breast	Radical amputation	6th dorsal vertebra	.....	.....	.....	.....	.....
38772	W	F	59	Scirrhous carcinoma	Right breast	Radical amputation	Upper end of right sacrum, right ilium	.....	12 months	.....	.....	Lost
38416	W	F	40	Scirrhous carcinoma	Right breast	Radical amputation	10th rib, left, posterior	.....	79 months	21½ months	X-rays	Lived 12 mo.
37870	W	F	45	Adenocarcinoma	Left breast	Amputation of breast	Skull, humeri, scapulae, clavicles, femora, all ribs, pelvis	.....	8 months	2 or 3 mo.	.....	Lived 12 mo.
37862	W	F	37	Fibrosarcoma	Right breast	Amputation of breast	4th and 5th cervical vertebrae	.....	40 months	16 months	Lead and radium	Lived 9 mo.
37824	W	F	58	Scirrhous carcinoma, left breast	Left breast	Radical amputation	Left ischium, upper third of left femur	.....	.....	.....	X-rays	Lived 26 mo. plus
37526	W	F	52	Scirrhous carcinoma	Left breast	Radical amputation	Skull, right sacro-iliac joint	.....	.....	.....	Lead and x-rays	Lived 12 mo.
37192	W	F	33	Scirrhous carcinoma	Right breast	Radical amputation	Long bones	.....	.....	47 months	X-rays (?)	Lived 9 mo.
37166	W	F	54	Scirrhous carcinoma	Left breast	Radical amputation	Right humerus, right femur, ilia, vertebra	.....	.....	.....	X-rays	.....
36988	..	F	49	Carcinoma	..... breast	Radical amputation	Left ilium, left iliac joint, acetabulum, upper third of left femur, upper third of right femur	Left ilium	.....	36 months	X-rays	Lived 12 mo.
36727	W	F	56	Scirrhous carcinoma	Left breast	Radical amputation	8th dorsal, 4th and 5th lumbar vertebrae ilia, acetabula, ischia, femora	.....	.....	.....	X-rays	Lived 11 mo.
36004	W	F	..	Carcinoma	Right breast	Radical amputation	6th and 7th thoracic vertebrae	.....	.....	86 months	X-rays	Lived 5 mo.
35879	W	F	36	Carcinoma	Right breast	None	Skull, spine	.....	24 months	.....	.....	Living 6 mo., 1916
35363	W	F	49	Carcinoma	Left breast	Not stated	Spine	.....	36 months	24 months	X-rays	Lived 24 mo.
35420	W	F	54	Carcinoma	Right breast	Radical amputation	Right ilium, upper part of femur, 5th lumbar, 7th and 10th thoracic vertebrae, left femur, pelvis	.....	.....	57 months	X-rays	Lived 24 mo.
34980	W	F	42	Scirrhous carcinoma	Right breast	Radical amputation	Left sacro-iliac joint, left ilium, 5th and 6th thoracic vertebrae	.....	27 months	9 months	X-rays	.....
34398	..	..	..	Carcinoma	Right and left breasts	Amputation of breasts	Upper third of femur	Femur	.....	.....	Exploration, fracture wired	Lived 9 mo.

TABLE 1.—*Cases of Carcinoma of the Breast with Metastases to Bone—Continued*

Path. No.	Color	Sex	Age	Primary Tumor	Location of Primary Tumor	Primary Operation	Location of Metastases	Pathologic Fracture	Interval Between Appearance of Tumor and Metastases	Interval Between Primary Operation and Metastases	Treatment of Metastases	Duration of Life Following Metastases
34100	W	F	..	Scirrhous carcinoma	Left breast	Amputation of breast	7th dorsal vertebra, cervical vertebra	.....	8 months	7 months	Radium x-rays	Lived 9 mo.
33514	W	F	..	Carcinoma	Left breast	Amputation of breast	Pelvis	.....	.....	33 months	X-rays	Lived 23 mo.
33050	W	F	41	Scirrhous carcinoma	Right breast	Radical amputation	All lumbar vertebrae, sacrum, pelvis, hip joints	.....	13 months	5 weeks	X-rays	Lived 6 mo.
32788	W	F	..	Carcinoma	..... breast	None	Lower end of femur	Femur	.....	.....	Rest in bed	Living 12 mo., 1924
32238	W	F	..	Cylindroma, carcinoma	..... breast	Radical amputation	1st lumbar vertebra	.....	.....	56 months	X-rays	Living 19 mo.
31688	W	F	37	Scirrhous carcinoma	Right breast	Radical amputation	Right femur, humerus, ischium, left humerus, radius, femur, skull, cervical vertebrae	(1) left femur; (2) right femur	.....	.....	Rest and splints for fractures	Lived about 14 mo.
31650	W	F	44	Scirrhous carcinoma	Right breast	Radical amputation	Right femur, left femur, skull, ilium, vertebrae	Right femur	2 months	Few days	X-rays, Glover's serum	Lived 38 mo.
31273	..	F	45	Carcinoma	Left breast	Radical amputation	3d lumbar vertebra	.....	.....	16 months	X-rays	Lived 9 mo.
30446	W	F	50	Scirrhous carcinoma	Left breast	Radical amputation	2d lumbar vertebra	.....	30 months	24 months	X-rays	Lived 71 mo.
30509	W	F	51	Scirrhous carcinoma	Right breast	Radical amputation	Left ilium	.....	.....	144 months	X-rays	Lived 48 mo.
30099	W	F	..	Scirrhous carcinoma	Right breast	Radical amputation	3d rib, anteriorly	.....	75 mo. plus	72 months	Resection of rib tumor x-rays	Lived 29 mo.
29851	W	F	..	Colloid carcinoma	Left breast	Amputation of breast	Skull, ribs on right side	.....	.....	.....	X-rays	Lived 21 mo.
28821	C	F	50	Carcinoma, inoperable	Right breast	None	6th and 7th dorsal vertebrae, right clavicle, right scapula	.....	.....	.....	.....	.....
28778	W	F	73	Carcinoma	Left breast	Radical amputation	Sternum	.....	132 months plus	About 132 months	.....	.....
28540	..	F	21	Comedocarcinoma	Left breast	Radical amputation	Spine	.....	15 months plus	15 months	.....	Lived 3 mo.

28465	W	F	47	Carcinoma, inoperable	Right breast	None	Skull, sternoclavicular joint	.....	24 months	.....	X-rays advised	Lived 17 mo.
27630	W	..	..	Carcinoma	..... breast	Not stated	1st lumbar vertebra	.....	.....	.....	.....	.....
26825	W	F	42	Scirrhous carcinoma	Right breast	Radical amputation	Left scapula, left humerus at junction of middle upper third	.....	25 months	13 months	X-rays	Lived 11 mo.
26329	W	F	57	Carcinoma	Left breast Right breast	Radical amputation Radical amputation	10th thoracic vertebra, 7th, 8th and 9th ribs on right side, humeri, skull, femora	Multiple rib fractures	.....	1st operation, 18 yr. 3 mo.; 2d operation, 3 mo.	Radium	Lived 26 mo.
26319½	W	F	..	Scirrhous carcinoma	Right breast Left breast	Amputation of breast Amputation of breast	Skull, ribs, 11th thoracic vertebra	.....	.....	1st operation, 48 mo.; 2d operation, 22 mo.	.....	Lived 19 mo.
25874	W	F	46	Scirrhous carcinoma	Right breast	Radical amputation	Lumbar spine, ribs	.....	.....	5 months	.....	.....
23559	W	F	42	Scirrhous carcinoma	Right breast	Radical amputation	Bone	.....	30 months	8 months	X-rays	Lived 8 mo.
23091	W	F	40	Scirrhous carcinoma	Left breast	Radical amputation	Upper third of the femur, two ribs	Femur	58 months	34 months	.....	Living 12 mo.
22580	W	F	45	Scirrhous carcinoma	Left breast	Radical amputation	Spine	.....	120 months	108 months	.....	Living 5 mo.
21266	W	F	50	Scirrhous carcinoma	Left breast	Radical amputation	Pelvic bones	.....	.....	.....	.....	.....
19536	W	F	59	Scirrhous carcinoma	Right breast	Radical amputation	Long bones	.....	.....	.....	.....	Lived 1 mo. plus
18760	W	F	59	Inoperable carcinoma	Left breast	None	Vertebrae	.....	.....	.....	.....	.....
18550	W	F	36	Scirrhous carcinoma	Left breast	Amputation of breast	2d lumbar vertebra	.....	12 months	7 months	X-rays (three times)	Lived 5 mo.
18188	W	F	..	Scirrhous carcinoma	Right breast	Amputation of breast	5th, 6th, 7th and 8th thoracic vertebrae, skull	.....	.....	15 months	.....	Lived 22 mo.
17629	W	F	63	Inoperable carcinoma	Left breast	Excision of breast	3d, 4th and 5th lumbar vertebrae, 4th and 5th ribs on right side	.....	.....	.....	Spine explored	Lived 13 mo.
16998	W	F	45	Scirrhous carcinoma	Right breast	Excision of breast, later excision of axillary glands	Spine, skull	.....	30 months	18 months	.....	.....
16406	W	F	46	Scirrhous carcinoma	Left breast	Radical amputation	Spine, right ilium	.....	45 months	33 months	.....	Lived 20 mo.

TABLE 1.—*Cases of Carcinoma of the Breast with Metastases to Bone—Continued*

Path. No.	Color	Sex	Age	Primary Tumor	Location of Primary Tumor	Primary Operation	Location of Metastases	Pathologic Fracture	Interval Between Appearance of Tumor and Metastases	Interval Between Primary Operation and Metastases	Treatment of Metastases	Duration of Life Following Metastases
16135	W	F	62	Scirrhous carcinoma	Left breast	Local excision of tumor, later radical ampuation	3d rib, left	.....	.....	18 months	Exploration of rib	.....
15894	..	F	49	Scirrhous carcinoma	Left breast	Radical amputation	Upper third of femur	Femur	19 months	8 months	Resection of head of femur	Lived 15 mo.
15646	W	F	37	Scirrhous carcinoma	Left breast	Radical amputation	Sternum	.....	173 months	140 months	Radium	.....
15318	W	F	45	Scirrhous carcinoma	Right breast	Radical amputation	Spine	.....	54 months	18 months	.....	.....
15015	W	F	59	Medullary carcinoma	Left breast	Radical amputation	Spine	.....	.....	.....	.....	.....
12761	W	F	37	Carcinoma	Right breast	None	Left tibia, sacrum, ilia, femora, skull	.....	.....	.....	.....	Lived 6½ mo.
11626	W	M	56	Colloid carcinoma	Right breast	Excision of tumor, later complete operation	Spine and entire skeleton	.....	17 months	12 months	.....	Lived 8 mo.
11477	W	F	40	Scirrhous carcinoma	Left breast	Radical amputation	Skull, left femur, left tibia, left ilium, lumbar vertebra	Left femur, 5 cm. below greater trochanter	7 months	A few days	.....	Lived about 24 mo.
11169	W	F	49	Scirrhous carcinoma	Right breast	Radical amputation	Pelvis	.....	.....	.....	.....	.....
11142	..	F	50	Scirrhous carcinoma	Right breast	Radical amputation	Spine	.....	.....	.....	.....	.....
11063	W	F	68	Scirrhous carcinoma	..... breast	Radical amputation	Spine	.....	.....	.....	.....	.....
10251	..	F	32	Inoperable carcinoma	..... breast	None	Pelvis, right femur	Femur	1 mo. (?)	.....	.....	Lived 1 mo. plus
9954	W	F	34	Scirrhous carcinoma	Left breast	Radical amputation	Lower end of femur	Femur	13 months	10 months	X-rays	.....
9839	W	F	32	Scirrhous carcinoma	Right breast	Radical amputation	Spine	.....	.....	.....	.....	.....
8952	W	F	58	Scirrhous carcinoma	Left breast	Radical amputation	4th lumbar vertebra	.....	24 months	18 months	.....	Lived 36 mo.
8886	W	F	60	Scirrhous carcinoma	Left breast	Radical amputation	Spine	.....	.....	.....	.....	.....

8175	W	F	57	Scirrhous carcinoma	Right breast	Radical amputation	Bone	.....	.....	.....	.....	.....
7261	W	F	55	Scirrhous carcinoma	Right breast	Radical amputation	Spine	.....	.....	.....	.....	.....
6470	W	F	70	Scirrhous carcinoma	Left breast	Radical amputation	Sternum	.....	.....	.....	.....	.....
6405	W	F	33	Carcinoma	..... breast	Amputation of breast	11th and 12th dorsal vertebrae	.....	54 months	15 months	.....	Lived 2 mo.
6318	W	F	42	Carcinoma	Left breast	Amputation of breast	Thoracic vertebra	.....	54 months	42 months	.....	.....
6300	W	F	45	Scirrhous carcinoma	Left breast	Radical amputation	Spine	.....	4½ months	2½ months	X-rays	Lived 5 mo.
5939	W	F	32	Carcinoma	Right breast	Radical amputation	Vertebra	.....	20 months	10 months	.....	Lived 4 mo.
5261	..	..	..	Medullary carcinoma	Left breast	Radical amputation	Hip	.....	12 months	0 months	.....	Lived 12 mo.
5144	W	F	39	Comedocarcinoma	Right breast	Radical amputation	3d thoracic vertebra	.....	21 months	15 months	Laminectomy of 2d and 3d dorsal vertebrae	Lived 3 mo.
4726	W	F	..	Scirrhous carcinoma	..... breast	Radical amputation	Spine	.....	.....	.....	.....	.....
4495	W	F	62	Scirrhous carcinoma	Left breast	Radical amputation	Spine	.....	.....	.....	.....	.....
4473	W	F	48	Scirrhous carcinoma	Left breast	Radical amputation	Sternum, ribs	.....	.....	.....	.....	.....
4305	W	F	50	Comedocarcinoma	Right breast	Radical amputation	Skull, thoracic and lumbar spine	.....	43 months	42 months	.....	Lived 3 mo.
3759	W	F	45	Carcinoma	Left breast	Radical amputation	Upper third of right humerus	.....	7 months	.....	Amputation of right arm at shoulder joint	Lived 18 mo.
2858	W	F	34	Scirrhous carcinoma	Right breast	Radical amputation	Spine	.....	114 months	90 months	.....	.....
2538	W	F	39	Scirrhous carcinoma	Left breast	Radical amputation	Spine	.....	60 months	24 months	.....	.....
1611	W	F	61	Scirrhous carcinoma	Right breast	Radical amputation	Left femur	Left femur	12 months (?)	6 months	.....	Lived 6 mo. plus
260	W	F	59	Carcinoma	Right breast	Radical amputation, operation for recurrence	Femur	Femur	20 years	1st operation, 19 yr. 8 mo.; 2d operation, 2 mo.	.....	Lived 8 mo. plus
93	C	F	60	Medullary carcinoma	Left breast	Radical amputation	Left femur	.....	48 months	36 months	Rest in bed	Lived 6 mo.
92	W	F	46	Scirrhous carcinoma	Left breast	Radical amputation	Head of femur	.....	68 months	18 months	.....	Lived 6 mo. plus

carcinoma of the bone, making a total incidence of 100 cases (table 1), or 5.2 per cent of all carcinomas of the breast in this study. Many of the patients living to date have not reached the five year period, and only the future can predict their clinical course.

Metastatic cancer from the breast in bone is a disease occurring in middle or late life. The majority of the lesions occur between the ages of 35 and 55, the extremes in age being 21 and 73 (fig. 1).

The bones most frequently involved are those of the spine, pelvis, femur, skull, ribs and humerus in the order given (table 2, fig. 2).

TABLE 2.—*Involvement of Bone in One Hundred Cases of Metastatic Carcinoma of the Breast*

Bone Involved	Number of Cases	Number of Times	Right	Left	Undetermined
Spine					
Cervical	3	2	..	..	1
Thoracic	13	23	..	..	2
Lumbar	14	17	..	..	2
Femur					
Upper third	16	20	7	8	5
Lower third	4	4	2	..	2
Head	2	3	1	1	1
Pelvis					
Ilium	15	19	8	8	3
Ischium	5	7	3	3	1
Sacrum	3	3	1	..	2
Sacro-iliac joint	3	3	2	1	..
Acetabulum	2	3	1	2	..
Pubes	1	2	1	1	..
Skull (frontal, parietal, temporal)	13	15	..	..	10
Ribs	13	10	4	2	7
Humerus					
Upper third	2	2	1	1	..
Head	2	3	2	1	..
Junction of middle and lower third	1	1	1	..	..
Junction of middle and upper third	1	1	..	1	..
Sternum	4	4	..	..	..
Entire skeleton	3	Multiple	..	..	..
Clavicle	3	4	2	2	..
Scapula	3	4	2	2	..
Tibia (upper third)	1	1	..	1	..
Radius (lower third)	1	1	..	1	..

While metastases were rarely found in the bones of the forearm and the lower part of the leg,[2] two such incidences are noted: one in the upper end of the tibia and the other in the lower end of the radius.

Prior to 1910, accurate information concerning the location of metastases was gained by necropsy and physical examination. In general, these statistics afforded only a trustworthy evidence in bones that were the common site of pathologic fracture, or that were easily accessible at the postmortem table. With the advent of the x-rays, roentgenograms

2. Osler, W.: Medical Aspects of Carcinoma of the Breast, Brit. M. J. **1**:1, 1906. Neal, M. P., and Robnett, D. A.: Generalized Osseous Metastases Secondary to Atrophic Scirrhous Carcinoma of Left Breast, Arch. Surg. **14**:529 (Feb.) 1927. Carnett and Howell (footnote 1, third reference). Handley (footnote 1, fourth reference).

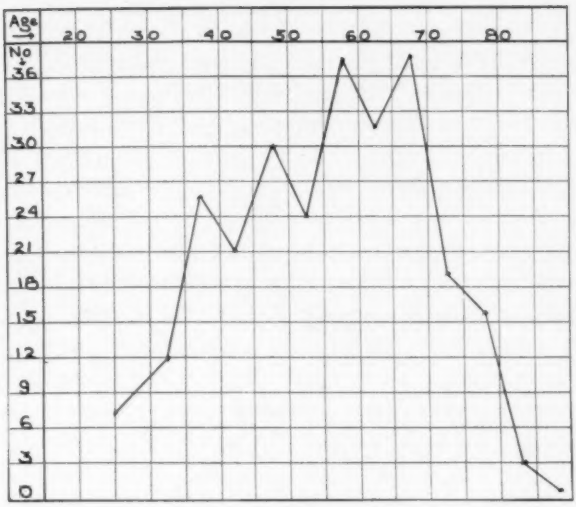

Fig. 1.—Age incidence of metastatic carcinoma and metastatic sarcoma in 339 cases with secondary involvement of the bone.

Fig. 2.—Distribution of carcinoma and sarcoma with metastases to bone according to skeletal location. The solid black areas indicate the most frequent sites; the checked areas, the common sites; the diagonal lines, the occasional sites, and the white areas, rare sites.

of the entire skeleton have permitted greater accuracy and have facilitated the study of the incidence of bony metastases in various parts of the skeleton. However, many bones, such as the sternum and ribs, can be demonstrated microscopically to be invaded by tumor, although the evidence may not appear in the roentgenograms. A comparison of statistics deduced by the older methods of examinations and those of more recent studies which are made up largely of roentgenologic examinations shows the greater value of the combined methods (table 3).

Symptoms.—Clinically, pain of a severe rheumatic character is an important feature. When these metastatic foci localize about the spine,

TABLE 3.—*Incidence of Bony Metastases*

	100 Cases*		73 Cases†	
	No. of Cases	Percentage of Total	No. of Cases	Percentage of Total
Spine	30	30	12	3.6
Pelvis	29	29	0	0.0
Femur	22	22	14	4.2
Ribs	13	13	28	8.0
Cranial bones	13	13	9	2.7
Humerus	6	6	9	2.7
Sternum	4	4	30	9.0
Clavicle	3	3	5	1.5
Scapula	3	3	1	0.3
Radius	1	1	0	0.0
Tibia	1	1	1	0.3
Ulna	0	0	0	0.0
Fibula	0	0	0	0.0
Patella	0	0	1	0.3
Bones of hand	0	0	1	0.3
Bones of foot	0	0	0	0.0

* From the Surgical Pathological Laboratory, 1930.

† From Sampson Handley: Cancer of the Breast and Its Operative Treatment, 1906.

girdle pains and neurologic manifestations, such as extramammary pain,[3] abdominal pain and pain in the sciatic nerve, numbness of the legs or arms, spastic paralysis or weakness of the various extremities are present. Loss of vesical control and weakness of the rectal sphincters are not infrequent signs. Often there are pains about the head associated with involvement of the skull, and two cases showed ocular changes, one unilateral exophthalmos and the other bilateral choking of the disks. Metastatic deposits in the extremities themselves often give severe, boring pains—stiffness of adjacent joints and swelling of the affected limb.

In the beginning, pain may be so mild and transient that it attracts little notice, and only after more ominous symptoms appear is medical

3. Ginsburg (footnote 1, seventh reference).

aid sought. The patient may be seized at the onset with excruciating pains requiring large doses of morphine, and occasionally pain precedes roentgenologic evidence of bony metastases from three to eighteen months.[3]

Pathologic fracture occurred in fifteen instances (15 per cent). Thirteen were in the femur, one in the ilium, and another case revealed multiple fractures of the ribs. As was pointed out in a previous communication,[4] among the malignant tumors of bone the greater number of pathologic fractures (62 per cent) were found in association with multiple myeloma, while other types of neoplastic lesions in bone similarly affected by fracture are, in the order of their frequency: cyst of the bone, 45 per cent; giant cell tumor, 14 per cent; osteogenic sarcoma, 8 per cent; and Ewing's sarcoma,[5] 5 per cent.

Patients show great variability in their constitutional response to invasion by the tumor. In some cases a rapid progress of the disease is noted with little or no attempt on the part of the body to react; while in others, with the assistance of various therapeutic aids, improvement occurs, and the patients are able to live useful lives for some time.

The blood picture is normal in most cases of early bony metastases; the majority of them eventually show a secondary type of anemia with its complications as the disease progresses. The leukocyte count is practically normal, save for a slight eosinophilia in a few instances—from two to four eosinophils per hundred cells. In the literature[6] an occasional case with bony metastases is reported, showing a pseudopernicious type of anemia with a color index over 1, a slight leukocytosis, nucleated red blood cells, myelocytes and myeloblasts. The ordinary anemia of cancer, according to Piney,[7] is not dependent on the presence of carcinomatous deposits in the marrow but on intrinsic changes in this tissue. Blood changes simulating those in pseudopernicious anemia have always been found in cases in which metastasis has been present for a sufficient time to permit hyperplasia of the marrow. Chemical examination shows that the blood is normal in most patients. An occasional trace of albumin is found in the urine, and in three cases Bence-Jones bodies were isolated.

4. Geschickter, C. F., and Copeland, M. M.: Multiple Myeloma, Arch. Surg. **16**:818 (April) 1928.

5. Copeland, M. M., and Geschickter, C. F.: Ewing's Sarcoma, Arch. Surg. **20**:258 (Feb.) 1930.

6. Epstein, J.: Blutbefunde bei metastatischer Carcinöse des Knochenmarks, Ztschr. f. klin. Med. **30**:121, 1896. Houston, T.: The Conditions that Simulate Pernicious Anemia, Brit. M. J. **2**:1257, 1903.

7. Piney, A.: Carcinoma of the Bone Marrow, Brit. J. Surg. **10**:235, 1922-1923.

The terminal phases of the disease reveal a progressive emaciation, often with much pain, and when the lungs are involved (nineteen cases), respiratory embarrassment with spitting of blood and paroxysms of coughing supervenes.

Internal metastases usually present themselves later than the secondary deposits to bone.

Roentgen Studies.—As depicted by the roentgenogram, lesions of metastatic carcinoma of the breast which have localized in the bone are most often multiple, presenting themselves as a single focus in only one fourth of the cases. The majority of these solitary metastases are in

Fig. 3 (path. no. 23091).—Roentgenogram of the upper third of a femur showing involvement of the greater trochanter and neck, one of the most frequent sites of metastases in this bone from carcinoma of the breast.

the vertebrae or femur, but it is very probable that if such cases were followed to their termination, lesions in other bones would appear.

Two types of metastatic lesions are noted in the x-ray films. The more common one is an osteolytic or bone-destructive lesion, while the other is a sclerosing or bone-forming process,[8] the latter occurring in outspoken fashion only twice in this series of cases, although it is not uncommon in bony metastases from carcinoma of the prostate.

8. Plank, T. H.: An Unusually Interesting Case, J. Radiol. **4**:247 (July) 1923. Ginsburg, S.: An Unusual Case of Osteoplastic Skeletal Metastases, Arch. Surg. **11**:219 (Aug.) 1925.

When a long bone such as the femur is involved, the portion affected is usually the proximal end. In the femur, the metastases occur most frequently about the greater trochanter and surgical neck (fig. 3), producing destruction of the bone with little evidence of repair. There is practically no periosteal reaction, the lesion appearing initially as a medullary involvement with subsequent destruction of the cortex from within. It is interesting to note that often the focus of tumor in the femur is well above the average entrance of the nutrient artery,[9] a fact cited by Handley [10] in favor of lymphatic permeation as a mode of metastases. This will be discussed subsequently.

Fig. 4 (path. no. 31650).—Involvement of the greater trochanter, neck and upper shaft of a femur showing increased density of the bone within the areas of destruction.

Sometimes mottling due to increased density of the bone occurs within the area of destruction (figs. 4 and 5), and a thickening of the cortex appears above or below the site of metastasis. This increase in density is found microscopically to be an attempt at repair of the bone or fibro-ostosis.[11] This reaction is often marked after roentgen therapy over the affected bone.

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9. Sobotta, J., and McMurrich, J. P.: Atlas of Human Anatomy, New York, G. E. Stechert & Company, 1927, vol. 1, pp. 1-98.

10. Handley (footnote 1, fourth reference).

11. Geschickter, C. F., and Copeland, M. M., with Foreword by Bloodgood, J. C.: Osteitis Fibrosa and Giant Cell Tumor, Arch. Surg. **19**:169 (Aug.) 1929.

Bloodgood [12] has pointed out that evidence of such formation of new bone may be used as a point in differential diagnosis in multiple tumors of the bone. When this formation occurs as mottling within an area of destruction in the bone, it favors the presence of a metastatic process as opposed to the more definitely punched-out areas of destruction seen in such lesions as multiple myeloma.

When the pelvis is implicated, the heads of the femurs may be involved, due to an extension of tumor from the pelvis along the ligamentum teres (fig. 6). The significance of such an associated involvement will be pointed out later in a discussion of the modes of metastases.

Fig. 5 (path. no. 35420).—Mammary carcinoma involving the greater trochanter and upper shaft of a femur with thickening of the cortex below the lesion and evidence of the formation of new bone within the area of destruction.

The entire femur may be involved with the riddling of the other bones, or rarely isolated deposits of tumor may appear in the lower third (fig. 7). The humerus, though less frequently affected, shows the same type of destruction either in the head, in the region of the nutrient artery which is located medially and opposite the attachment of the deltoid muscle, or in the bone, which may be diffusely involved.

12. Bloodgood, J. C.: Bone Tumors, Benign and Malignant: A Brief Summary of the Salient Features Based Upon the Study of Some Three Hundred and Seventy Cases, Am. J. Surg. **34**:229 (Sept.) 1920.

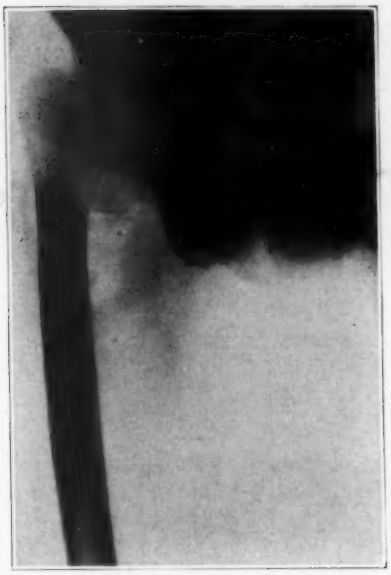

Fig. 6 (path. no. 40002).—Roentgenogram of the pelvis and upper third of a femur showing the associated involvement of pelvis and femur which is due to an extension of the tumor from the pelvis along the ligamentum teres.

Fig. 7 (path. no. 31688).—Roentgenogram of the lower third of a femur showing involvement of the inner aspect of the lower shaft.

Recently, Carnett and Howell [13] have shown that the humerus together with the shoulder girdle is affected more frequently than has been found in the present series. But among the cases studied by these authors, radical operation for the complete removal of the breast was rare, whereas in the series of cases from this laboratory, 75 per cent were subjected to the radical operation from four to eighteen months before metastases appeared. In the cases that received radical operation, the greater part of the lymphatic drainage adjacent to the seat of the primary tumor was interrupted, and the likelihood of a regional spread of the disease was greatly reduced.

The pelvis, vertebrae, skull, ribs, scapula, clavicle and sternum, which represent the other bones usually affected, showed the same typical medullary destruction with punched-out areas not unlike those seen in multiple myeloma (figs. 8 and 9). The tendency of these areas to become confluent and to be fringed by bone of increased density is frequent when the involvement of the skeleton is diffuse. In such cases the lack of distortion or bending of the bones, despite the degree of pathologic change, is outstanding. Failure for such distortion to take place is due partially to the advanced stage of the disease which confines the patient to bed, and to the fact that roentgen therapy is so frequently resorted to; also, the age of the patient is responsible for a degree of brittleness of the bones which makes fracture rather than bending the rule. In one case, the lower end of the radius showed a punched-out area in its lower portion near the region of the epiphyseal line and on the medial side of the bone. Above it, a slight irregular mottling is noted in the cortical and medullary area (fig. 10).

Solitary areas of metastatic carcinoma may be simulated by a latent cyst of the bone (fig. 11), a solitary focus of multiple myeloma (fig. 12) or by the osteolytic form of osteogenic sarcoma (fig. 13). The latent cyst of the bone is to be distinguished from metastatic carcinoma by the distinct signs of ossification present in the bone shell, and the thickness and competent defensive reaction visible in the areas surrounding the walled-off cavity. The latent cyst of the bone is nearly always without symptoms clinically, whereas pain and dysfunction of the part occur as a rule with the metastatic lesion.

In the roentgenogram it may be practically impossible to distinguish between multiple myeloma and diffuse metastatic carcinoma. Both may be central destructive lesions of the bone which gradually erode the cortex from within outward. Bence-Jones bodies in the urine in cases of multiple myeloma, 65 per cent, however, occur more frequently than in cases with metastatic carcinoma from the breast, 4 per cent.

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13. Carnett and Howell (footnote 1, third reference).

Fig. 8 (path. no. 37870).—Roentgenogram of the upper third of a humerus with the other bones of the shoulder girdle and ribs, showing punched-out areas not unlike multiple myeloma.

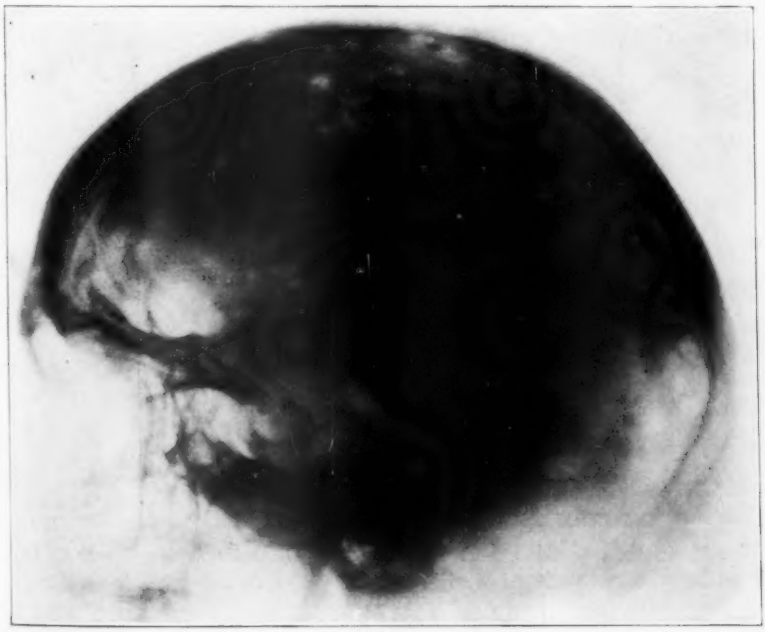

Fig. 9 (path. no. 37870).—Skull showing metastases from carcinoma of the breast simulating multiple myeloma.

Fig. 10 (path. no. 31688).—A lesion in the lower end of the radius represented by a punched-out area in the region of the epiphyseal line and on the medial side of the bone.

Fig. 11 (path. no. 42526).—A latent cyst of the bone in the lower end of a tibia which may be confused with solitary areas of metastatic carcinoma.

Fig. 12 (path. no. 42108).—A solitary focus of multiple myeloma which may be confused with metastatic carcinoma when it is situated in a bone as a single lesion.

Fig. 13 (path. no. 37614).—Roentgenogram of a femur showing the osteolytic form of osteogenic sarcoma, not infrequently confused with the roentgenographic picture of metastatic carcinoma.

Fig. 14 (path. no. 37870).—A longitudinal section of a humerus showing involvement by metastatic mammary carcinoma. A cyst may be seen in the upper shaft filled with dark, pigmented, jelly-like material.

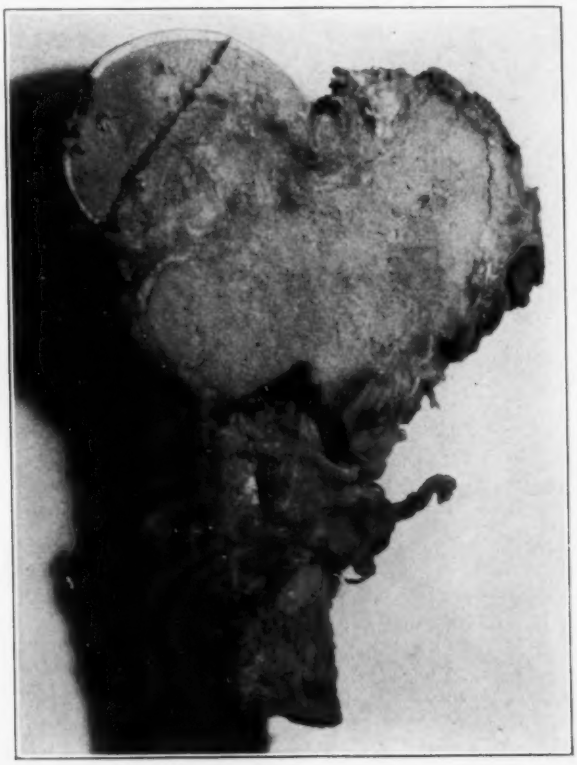

Fig. 15 (path. no. 40002).—A longitudinal section of the upper third of a femur showing areas of metastatic carcinoma just beneath the minor trochanter where pathologic fracture had occurred, and in the region of the fovea capitis other deposits are seen.

The osteolytic type of osteogenic sarcoma may produce an area of destruction of the bone similar to that in metastatic carcinoma. Such an area shows a greater inclination to be asymmetrically located in the bone and shows evidence of its more rapidly destructive character.

Pathologic Changes.—Of the gross material at hand, the femur and the humerus offer the most valuable information in the interpretation of the roentgen observations, and in analyzing the modes of metastases.

The humerus is involved principally in the medullary and cortical areas (fig. 14), the medullary cavity in the upper portion of one

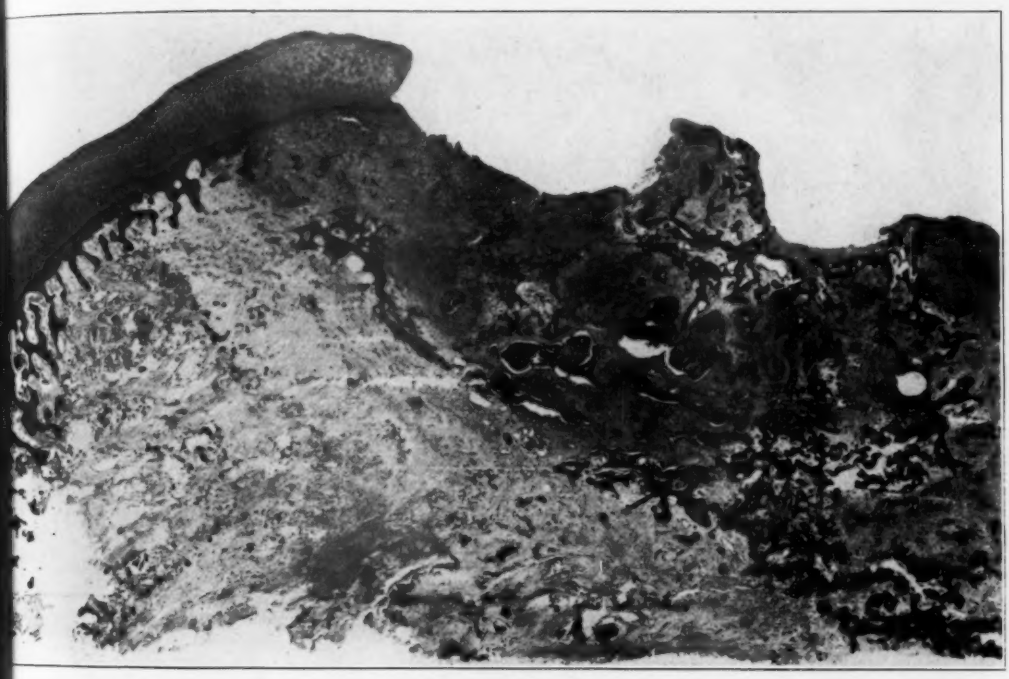

Fig. 16 (path. no. 40002).—Low power photomicrograph of an area in the region of the fovea capitis taken from the head of the femur depicted in figure 15. Note the infiltration of epithelial cells from above downward and the area of fibrous tissue reaction below the tumor invasion. The joint cartilage is intact on either side of the tendinous attachment.

humerus being practically replaced by carcinomatous tissue, the tumor extending well up into the head with discrete tumor nodules appearing in the spongy bone just beneath the articular cartilage. Below the region of the greater tuberosity, the entire cortex is destroyed, while rather substantial bone is found in the region and just medialward to this point. In the upper shaft of the bone, a cystic area with a chocolate colored wall is seen, the result of the absorption of hemorrhage.

In one instance, the majority of the deposits of tumor were found in the upper portion of the head around the greater tuberosity and beneath the articular cartilage extending down toward the shaft, interrupted by a rather well preserved area of spongy bone. Beneath this area of

Fig. 17 (path. no. 40002).—Photomicrograph showing nests of epithelial cells in a fibrous stroma with occasional small spicules of old bone undergoing destruction by direct attack of the tumor cells.

spongy bone, further down in the shaft, the medullary cavity was found to be filled with tumor tissue, the vertebrae in this case showing focal deposits in the peripheral portion of the bone.

The femur most often showed metastases in the head and in the region of the great tuberosity with extension down into the shaft. In one case, a pathologic fracture had occurred just beneath the minor trochanter, at which point a cellular area of tumor deposit existed. In the region of the fovea capitis, another cellular deposit was found (fig. 16) extending along beneath the articular cartilage down to the greater trochanter, the distance of which had been much shortened due to the telescoping of the head on the neck. Other femurs showed less extensive deposits in these same areas. The microscopic examination of sections taken from various points in these bones revealed destruction of the spongy and cortical bone by direct contact of the tumor cells with the bone and to a lesser extent by the activity of the osteoclasts destroying spicules of dead bone. Regardless of how the tumor cells reach the skeletal system, the progress in the bone seems to be via the medullary cavity and the haversian canals, beginning in those areas in which red marrow is present.

Sections taken from the head of the femur illustrated in figure 15 show large nests of epithelial cells in a fibrous stroma with occasional small spicules of old bone undergoing destruction by direct attack of the tumor cells (figs. 16 and 17).

Abundant evidence is found microscopically in favor of a natural tendency of bone to react by direct transition of fibroblasts to osteoblasts to osteoid tissue in an effort to protect itself from further invasion and to rebuild that part already destroyed (fig. 18). Areas of fibro-ostosis (a reaction to the invasion of cancer) are seen, with strands of fibrous tissue being transformed into osteoblasts and osteoid tissue, bordering on small nests of epithelial cells distributed throughout this reactive process. In cases in which roentgen therapy has been given with beneficial results, microscopic analysis of the affected bone reveals a marked increase in the fibrous tissue reaction and a transformation of this tissue into the osteoid type of bone. Cancer cells can be seen crowded between the fibrous strands (fig. 19).

Treatment.—A survey of the treatment received by patients with primary carcinoma of the breast and a study of the rate of dissemination of the cancer expressed in the interval of time between the first appearance of the tumor and metastases and also between the primary operation and the subsequent metastases throw some light on the results that can be obtained by resection alone or by resection and radiation or by radiation alone of the affected bones.

For purposes of analysis, the patients have been divided into the following groups: (1) those who first had a radical amputation of the breast; (2) those who had only simple amputation of the breast or local

excision; (3) those on whom no operation was performed and who only received various forms of palliative treatment.

In group 1 there are seventy-four patients with radical amputation of the breast, showing subsequent metastases to bone. The average

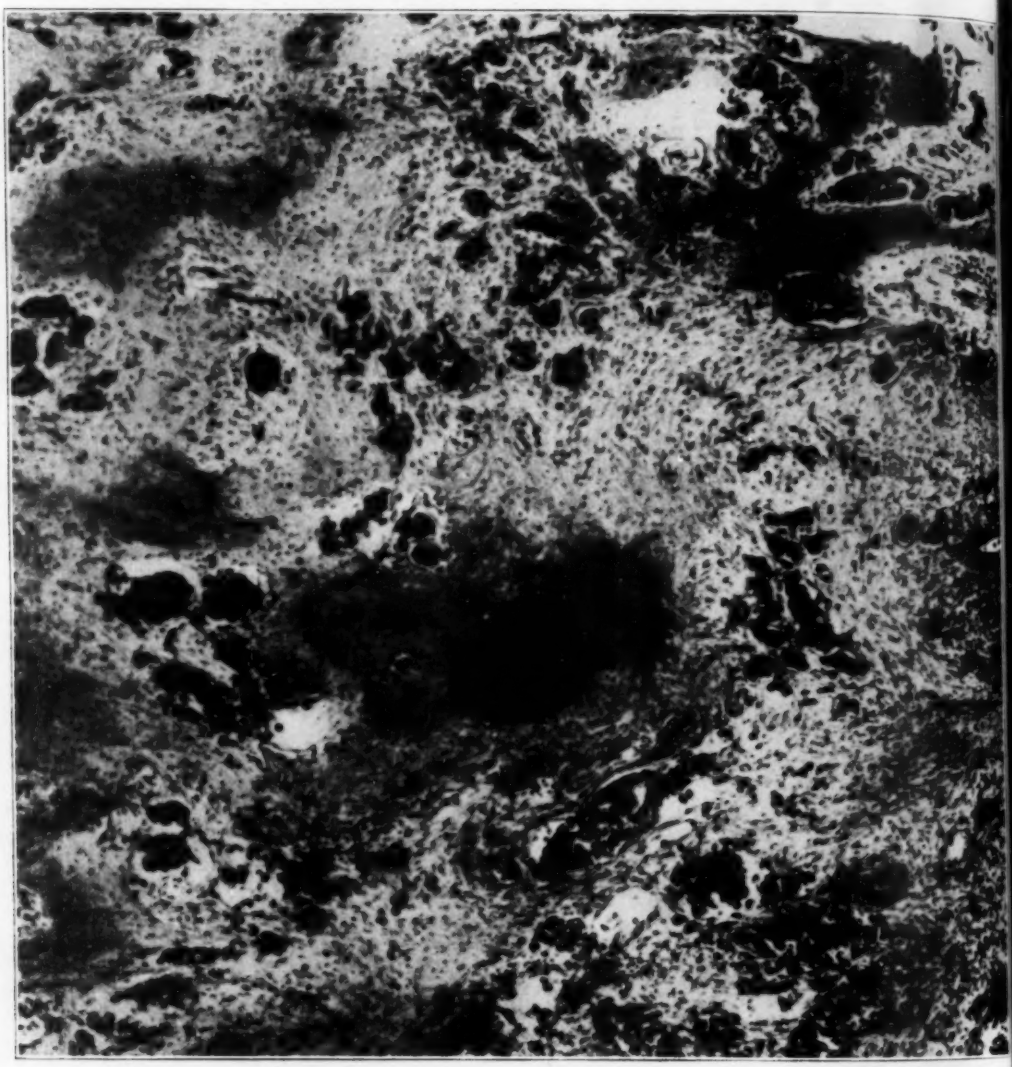

Fig. 18 (path. no. 12761).—Photomicrograph showing areas of fibro-ostosis with strands of fibrous tissue being transformed into osteoblasts and osteoid tissue, bordering on small nests of epithelial cells distributed throughout this reactive process.

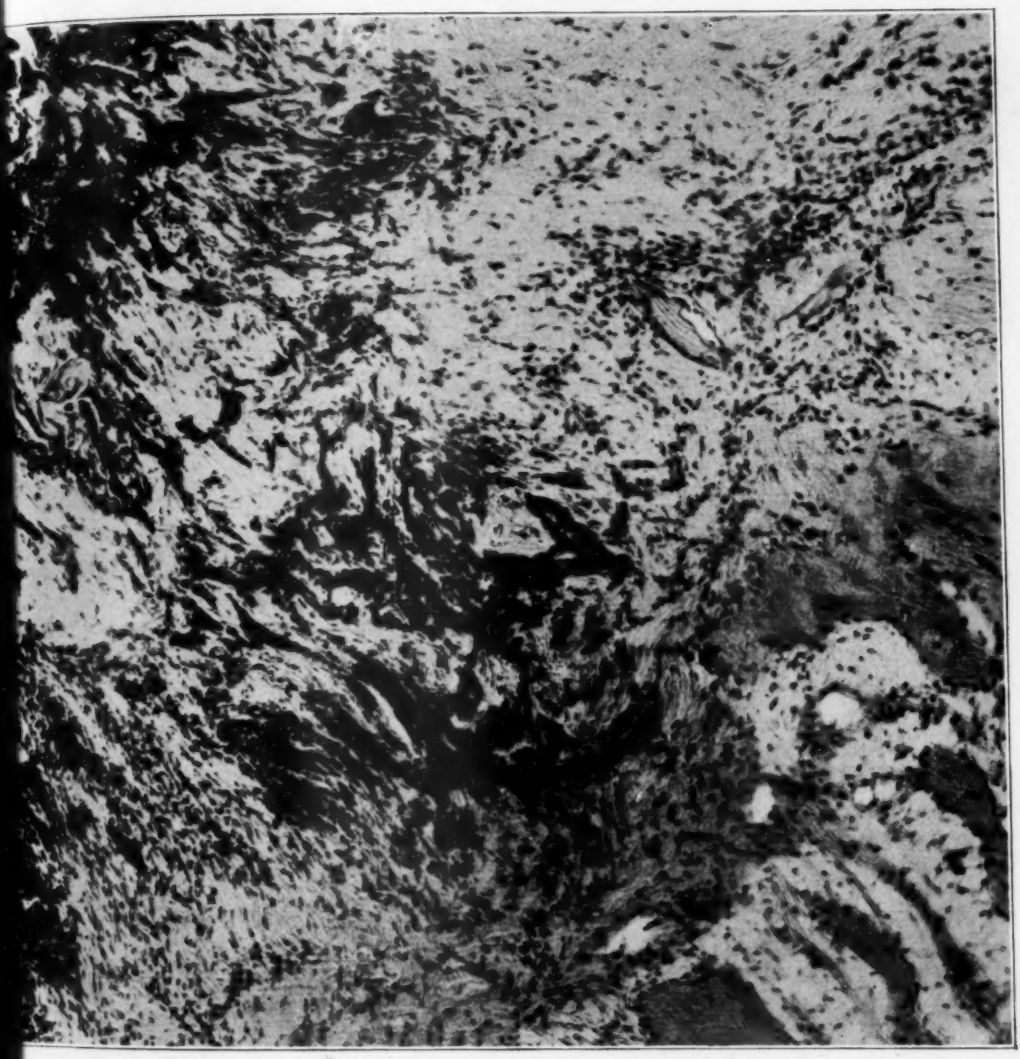

Fig. 19 (path. no. 34100).—Photomicrograph showing the effect of roentgen therapy on the structure of the bone invaded by tumor. Note the healing bone reaction (fibro-ostosis). Cancer cells can be seen crowded between the fibrous strands.

interval between the appearance of the primary tumor and the first evidence of metastases to bone was thirty-two and one-half months. In a few exceptional cases not included in this average, lesions of the bone developed at intervals as late as from nine to twenty years. If these exceptional cases are omitted, the time between radical removal of the breast and metastases averages thirty months. The tumors in the patients in group 1 were principally of the scirrhus type. Microscopic examination showed: scirrhus carcinoma, fifty-two cases; medullary carcinoma, four; comedocarcinoma, three; adenocarcinoma, three; and colloid carcinoma, one, with eleven unclassified.

Group 2 is represented by eighteen cases with a simple amputation of the breast or local excision. The average interval between the appearance of the primary tumor and the first evidence of metastases was twenty-nine and one-tenth months, while that between the operation and osseous involvement was sixteen and seven-tenths months. On microscopic examination, the histology of the primary tumors in this group were: unclassified, seven; scirrhus carcinoma, six; adenocarcinoma, three; colloid carcinoma, one, and fibrosarcoma, one.

Group 3, or the inoperable group, contained eight cases. The interval between the appearance of the primary tumor and the metastases ranged between one and twenty-four months.

The treatment as outlined here is based on the clinical experience of Drs. J. C. Bloodgood and Max Kahn. The roentgen treatment as given in this clinic consists of twelve thirty-minute exposures, using 200 kilovolts and 5 milliamperes, filtered through a combined 0.75 millimeter copper and 1 mm. aluminum filter, a 25 cm. diaphragmatic opening and 50 cm. focal distance. A total of ninety minutes is given over each area at periods of thirty minutes on consecutive days, each affected lesion being treated through four portals of entry. If further treatment is indicated, the foregoing procedure is repeated after a free interval of three months or more, depending on the condition of the patient.

While some of the treatments were given at other clinics, in the majority of instances the treatment was the equivalent of that given here, making the type of treatment fairly uniform in the various cases.

In group 1, those patients treated by radiation following the appearance of metastatic lesions of the bone had an average duration of life of eighteen months, two patients having survived the metastases for forty-eight and seventy-one months, respectively, while some lived as long as from one to two years. Among those not irradiated, the duration of life after metastases averaged eleven and one-half months.

In group 2, the average duration of life in persons with metastases who received roentgen treatment was sixteen and one-half months as compared with twelve and eight-tenths for those who did not receive irradiation.

In group 3, the patients who received radiation lived ten months, and those who did not receive radiation, seven and eight-tenths months.

Statistics on the various tumors metastasizing to bone show that the duration of metastases is essentially the same as in the aforementioned cases.

Resection of the affected part apparently had no effect on the duration of life, but gave relief from excruciating pain which is experienced in the diseased bone.

A number of observers [14] reported favorable results from roentgenotherapy in metastatic carcinoma of the bone. Irradiation is effective both in relieving pain and in accelerating repair of the bone of the affected skeleton, apparently reducing the invasive powers, at least temporarily, of the deposits of the cancer. In this series of cases, many patients were relieved from pain for varying intervals of time, and in four cases marked formation of new bone was noted with relief from pain and increased usefulness of the affected bone.

It would seem, therefore, that patients with carcinoma of the breast metastasizing to bone, when treated by roentgen therapy, may expect relief from pain and often a few months of fairly comfortable living, thus making the procedure one of definite benefit. In refractory cases, resection of the affected portion of the bone, where feasible, may be indicated for the relief from pain.

HYPERNEPHROMA

The great majority of hypernephromas are primary in the substance of the kidney, although they may develop in other regions.[15] Grawitz, in 1879, was one of the first to describe such a tumor,[16] and in 1898 the term hypernephroma was applied to the neoplasm by Birch-Hirschfeld.[17]

There is a feeling among pathologists that hypernephroma has a special predilection for the bones, but from an investigation of the literature it is difficult to form any definite idea as to the incidence of osseous involvement.

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14. Levin, I.: The Prognostic and Therapeutic Significance of Skeletal Metastasis in Cancer of the Breast, Ann. Surg. **65**:326, 1917. Kelly, H. A., and Fricke, R. E.: Problems in Treatment of Carcinoma of the Breast, Surg. Gynec. & Obst. **38**:399, 1924. Ginsburg (footnote 1, seventh reference).

15. Gibson, A., and Bloodgood, J. C.: Metastatic Hypernephroma with Special Reference to Bone Metastases, Surg. Gynec. & Obst. **37**:490, 1923.

16. Grawitz, P.: Ueber maligne Osteomyelitis und sarkomatöse Erkrankungen des Knochensystems als Befunde bei Fallen von perniciöser Anämie, Virchows Arch. f. path. Anat. **76**:353, 1879.

17. Birch-Hirschfeld, F. V.: Sarkomatöse Drüsengeschwülst der Niere im Kindesalter, Beitr. z. path. Anat. u. z. allg. Path. **24**:343, 1898.

TABLE 4.—*Cases of Hypernephroma with Metastases to Bone*

Path. No.	Color	Sex	Age	Primary Tumor	Location of Metastases	Pathologic Fracture	Treatment of Metastases	Duration of Metastases
49373	W	M	40	Hypernephroma	Right 6th rib	.....	X-rays	.....
42906	W	M	55	Hypernephroma	Upper end of right humerus	Humerus	X-rays, resection of upper end of humerus	Living 22 mo.
42704	W	M	26	Hypernephroma	Left ilium	.....	X-rays, exploration	Living 3 mo.
38324	W	M	55	Hypernephroma	Bones of foot	.....	Excision of part of tumor	Living 6 mo., 1926
37088	W	M	62	Hypernephroma	Upper third of right humerus	.....	X-rays, amputation of right arm	Living 7 mo. 5 days, 1926
36524	W	M	66	Hypernephroma	2d, 3d and 4th right ribs, 6th thoracic and 3d lumbar vertebrae	2d, 3d and 4th right ribs	Supporting cast for back	Lived 6 mo.
35762	W	M	82	Hypernephroma	Lower end of right femur	Femur	.....	Lived 9 mo.
35512	W	M	48	Hypernephroma	Tarsal and metatarsal bones of left foot	.....	Exploration, amputation of left foot	Living 6 mo., 1924
35416	W	M	..	Hypernephroma	Upper end of right femur	Femur	.....	.....
34362	W	M	56	Hypernephroma	Upper end of right humerus	.....	Amputation of right arm	Living 6 mo., 1921
32974	W	M	40	Hypernephroma	6th right rib	.....	X-rays, biopsy	.....
31887	W	F	52	Hypernephroma	Upper end of left femur, left ischium	Femur	Resection of head of femur, bone graft	Lived 10 mo.
30983	W	M	..	Hypernephroma	4th lumbar vertebra, right sacro-iliac joint, right ilium, skull, (parietal region)	.....	X-rays, erysipelas and prodigiosus toxins (Coley's)	Lived 5 mo.
30631	W	F	69	Hypernephroma	Skull, right temporal bone, left parietal bone	.....	Radium	Lived 34 mo.
29485	C	F	37	Hypernephroma	Upper end of femur	Femur	.....	.....
29461	W	F	55	Hypernephroma	Midshaft of right humerus	Humerus	Amputation of right arm	Lived 18 mo.
29397	W	M	28	Hypernephroma	All the lumbar verterbrae, all dorsal vertebrae, 2d cervical vertebra, 3d left rib, shaft of both humeri, upper end of femora	Lower end of femur	Hibb's operation	.....
27964	W	M	30	Hypernephroma	Head, shaft, left humerus	.....	Radium	Living 76 mo., 1927
6930	W	M	..	Hypernephroma	Humerus	.....	Operation (?)	.....
6290	W	M	52	Hypernephroma	Left sternum, upper end of femur, ribs	Femur	.....	.....
2250	W	M	45	Hypernephroma	Femur, humerus, dorsal vertebrae	Humerus	.....	.....
1415	..	..	..	Hypernephroma	Head of tibia	.....	.....	.....

Among the sixty-three persons affected by hypernephroma registered in this laboratory, there are twenty-two instances (34.9 per cent) with metastases to bone (table 4). The age incidence ranges between 21 and 81; the peak of incidence is about the sixth decade. The bones usually affected in the order of their frequency are: humerus, spine, femur, pelvis, ribs, bone of foot, skull and sternum (table 5).

Symptoms.—The lesion of the bone may be the first indication of the presence of the tumor in the body, as illustrated by the following case report (fig. 20):

TABLE 5.—*Involvement of the Bone in Twenty-Two Cases of Hypernephroma*

Bone Involved	No. of Cases	No. of Times	Right	Left	Undetermined Side
Humerus					
Location (?)	2	3	..	2	2
Upper third	4	4	3	1	..
Shaft	2	3	1	1	1
Femur					
Upper third	4	4	1	2	1
Middle third	1	1	1	..	..
Lower third	1	1	1	..	..
Spine					
Location (?)	1	1	..	..	1
Cervical	1	1	..	..	..
Thoracic	3	13	..	..	1
Lumbar	3	7	..	..	..
Ribs	5	6	2	1	2
Pelvis					
Ilium	2	2	1	1	..
Ischium	1	1	..	1	..
Sacro-iliac joint	1	1	1	..	..
Bone of foot	2	..	..	1	..
Skull	2	3	1	1	1
Sternum	1	1	..	..	..
Tibia	1	1	..	..	1

A white man, aged 55, eleven years previously while in France had an attack of arthritis in the right shoulder which lasted one month; in addition, the left knee, both ankle joints, the wrists and the right elbow joint were involved. Following much needed dental work, the arthritic symptoms disappeared except during changes in the weather, when they continued to be present in the right shoulder.

Twenty months before presenting himself for examination, the patient began to have definite pain about the head of the right humerus, with slight limitation of motion in the right shoulder ten months later.

A roentgenogram was made in March, 1929, which showed an area of destruction of the upper shaft of the humerus just below the head, about the size of a silver dollar, mostly on the outer aspect of the humerus. In June, July and September, 1929, other roentgenograms were made showing the progressive nature of the destructive lesion. The first evidence of the pathologic fracture was noted

in the roentgenogram made in 1930 (fig. 20, *C*), associated with a fair-sized tumor of the soft part. Roentgen therapy had been administered in adequate doses on four occasions with some slight remission in the excruciating pain, but with no great relief. Considerable morphine was needed to allay the patient's suffering. Other bones in the body were examined but no significant defects were made out, nor were there symptoms suggestive of other lesions in the skeletal framework. Repeated examinations of the urine and of the blood revealed nothing abnormal.

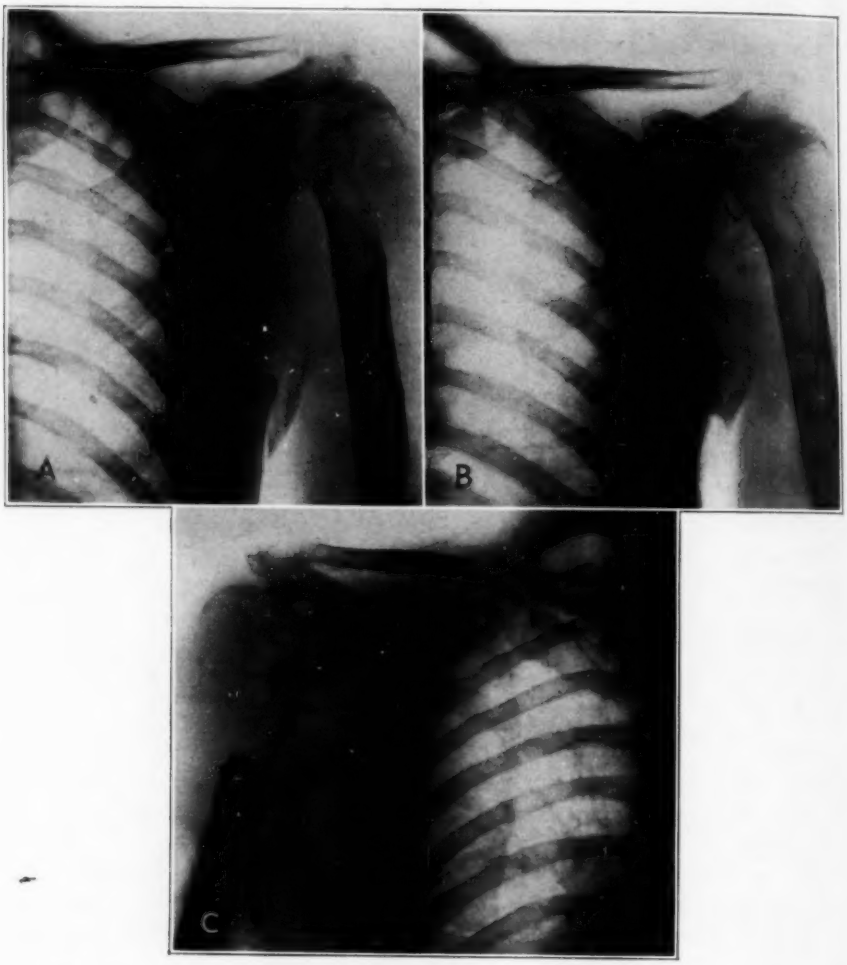

Fig. 20 (path. no. 42906).—*A*, roentgenogram of the upper end of a humerus showing marked destruction in the region of the surgical neck and upper shaft from metastatic hypernephroma. *B*, roentgenogram showing the progressive nature of the metastatic lesion in the head of a humerus taken three months after *A*. *C*, the complete destruction in the region of the surgical neck and the resultant pathologic fracture. This roentgenogram was taken about nine months following *A*.

In January, 1930, at a neighboring hospital, aspiration of the shoulder was done and only blood obtained. In May, 1930, Dr. Bloodgood resected the diseased head of the right humerus (fig. 21), which on microscopic examination (fig. 22) proved to be the seat of a hypernephroma. Operative recovery was uneventful, and before leaving the hospital the patient had practically abandoned the use of

Fig. 21 (path. no. 42906).—A gross specimen in longitudinal section showing metastatic tumor involvement from hypernephroma in the region of the surgical neck of a humerus, extending into the epiphysis, with total destruction of the cortex but no involvement of the joint cartilage. Note the subperiosteal invasion.

morphine, with complete relief from pain. Following the diagnosis of hypernephroma microscopically, a special examination was made of the kidneys, but no evidence of any lesion could be made out.

It has now been twenty-two months since the definite onset of symptoms, and the patient is doing very well.

Pathologic fracture occured in ten cases (45.4 per cent), six times in the femur, three times in the humerus, and in one instance multiple fractures of the ribs were found. Most of the fractures occurred in the upper third of the long bones. In one instance, spontaneous pathologic fracture was the first symptom referable to the disease.

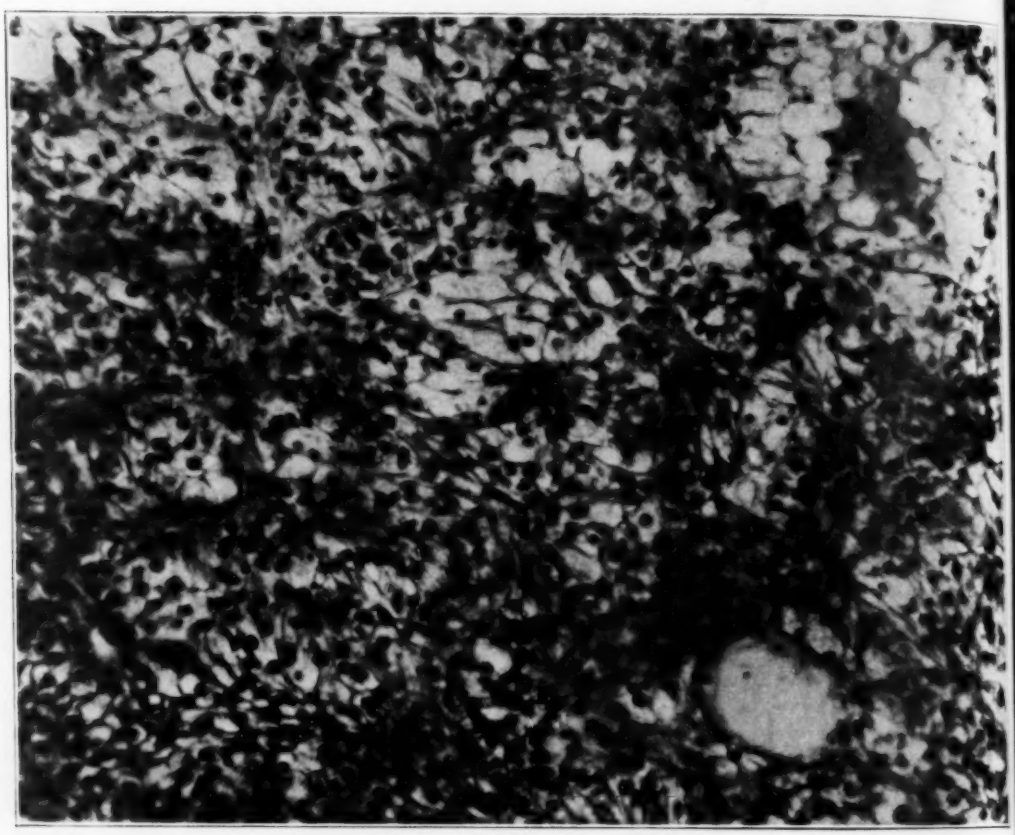

Fig. 22 (path. no. 42906).—Photomicrograph of the tumor depicted in figure 21, showing the typical structure of hypernephroma of the renal type, the cells are granular or foamy and the cytoplasm is remarkably clear. There is no evidence of fibro-ostosis.

As in metastases of the breast, the constitutional response of patients with metastatic hypernephroma of the bone is variable. True to the nature of metastatic lesions, pain of a rheumatic character is a leading symptom, and with spinal involvement many neurologic manifestations may be present. The blood picture eventually shows a secondary anemia, and the patients decline in weight, suffering from

progressively severe pains in the various bones affected. In three cases, the urine showed Bence-Jones bodies.

Roentgen Studies.—The lesions of the bone may appear in the roentgenogram either as single (fig. 20) or multiple lesions (fig. 23) located in one or more bones. In thirteen cases (59 per cent), the

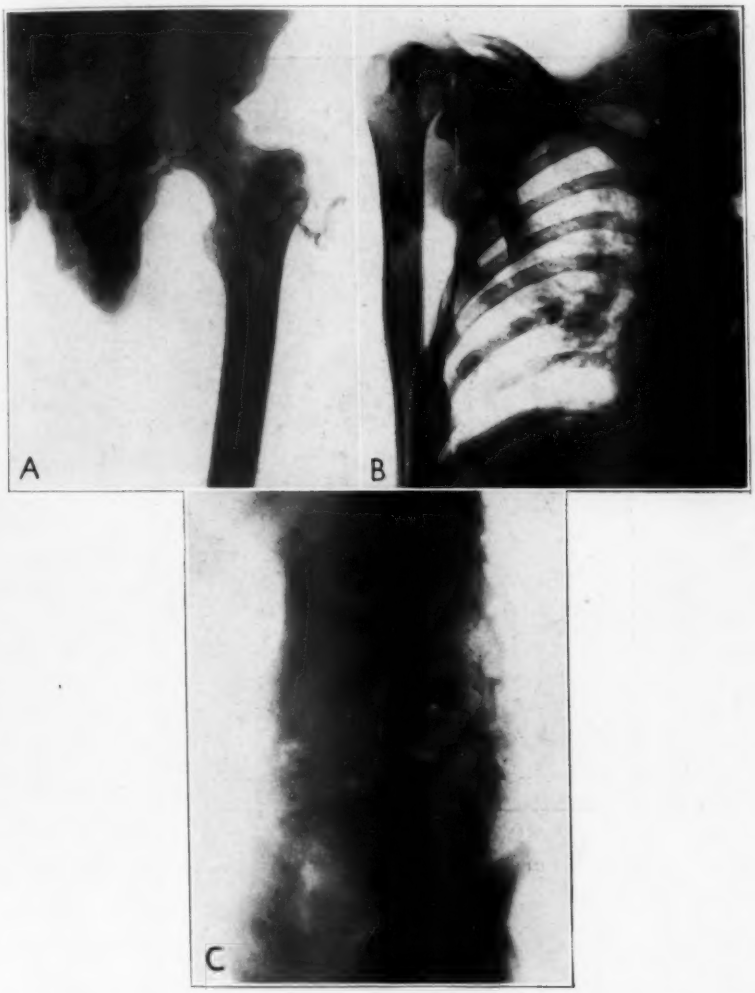

Fig. 23 (path. no. 29397).—Multiple foci in the skeleton which may be seen in metastatic hypernephroma. *A*, roentgenogram of the upper end of a femur showing metastatic involvement with an associated lesion in the adjacent pelvis and a slight tendency toward the formation of new bone within the destroyed areas. *B*, tumor invasion of the upper shaft and head of a humerus. *C*, destruction of the lumbar-vertebrae with practically no tendency toward the formation of new bone within the destroyed areas.

secondary deposit of bone was found as a single focus; in the majority of cases it appeared in a long bone.

It is noteworthy that many of these lesions are at the site of the nutrient vessels (fig. 24) as well as in the head of the humerus (fig. 20, *A*) and femur, together with an associated lesion of the pelvis (fig. 23, *A*). There is no evidence in bony metastases from hypernephroma that any marked attempt at fibro-osteosis or formation

Fig. 24 (path. no. 29461).—A metastatic lesion depicted in the roentgenogram of a humerus at the site of the nutrient vessels showing marked destruction of the bone with expansion.

of new bone takes place within the area of destruction. The lesion is a destructive one in the shaft or the head of the long bones, and in the bodies of the vertebrae, in the membranous bones of the skull and in the small bones of the feet. The earliest sign of involvement is always a distinctly medullary defect which destroys the cortex from within, with little or no expansion. Although the growth readily extends into the soft parts, periosteal changes in the roentgenogram are an exception. In many instances, the viscera have not been invaded. It

is the impression in this laboratory that with small local growths of the tumor in the kidney there is a greater tendency toward dissemination to the bone, whereas larger local proliferations of the tumor are less likely to show skeletal involvement.

The differential diagnosis from the standpoint of roentgenology is similar to that of metastatic lesions of the bone in general, which have been detailed under carcinoma of the breast. In contrast to metastatic tumors from cancer of the breast, lesions of the bone in hypernephroma show a greater tendency to occur as a single focus and to be practically always osteolytic.

The gross appearance of the tumor as seen in the bone is well exemplified in figure 21. The growth always has a characteristic brownish-yellow color, flecked with red. When seen in the head of a long bone, there is marked destruction of the cortex with diffuse involvement of the medullary cavity and the spongy bone of the epiphysis. The cartilage of the joint does not seem to be affected, but the tumor pushes up beneath the periosteum in the area of cortical bone.

In the medullary cavity, in many cases, little deposits of brownish tumor can be seen. Where the shaft is involved at the site of the nutrient vessels (fig. 24), there is destruction of the cortex with tumor in the subperiosteal area, and at the attachment of the deltoid muscle which exerts a tensile influence on the bone, there is often evidence of a pathologic fracture with some invasion of the muscle tissue. Studies of the muscle tissue taken at points some distance from the site of invasion by the tumor reveal no tumor cells. This type of tumor occurring as a single focus lends proof to the embolic theory of metastases.

Further evidence is found in the literature to substantiate this mode of invasion of the bone. Albrecht [18] reported a case in which there was a single lesion noted in the scapula four years after nephrectomy for hypernephroma. Ten years later, following resection of the scapula, the patient was still well. On the other hand, permeation of the lymphatics by tumor cells is undoubtedly a mode of progression in this tumor.[19]

The microscopic picture as seen in figures 22 and 25 is typical of the ordinary structure of hypernephroma of the renal type. There apparently is little tendency on the part of the bone to wall off the tumor. In a few areas there are spicules of old bone being destroyed by direct contact with the tumor cells. The cells are granular or foamy, and are interspersed with granules of lipoid. The cytoplasm is usually

18. Albrecht, P.: A Study of the Clinical and Pathological Anatomy of Hypernephroma, Arch. f. klin. Chir. **76**:1073, 1905.

19. LeCount, E. R.: Report of a Case of Malignant Hypernephroma, Tr. Chicago Path. Soc. **5**:82, 1901-1903. Bierring, W. L., and Albert, H.: Secondary Manifestations of Hypernephromata, J. A. M. A. **43**:234 (July 23) 1904.

remarkably clear, containing large globules of fat; the amount and clearness of the cytoplasm depends on the grade and rapidity of the growth.

Treatment.—The proof of the benefit of any one form of treatment depends on the ultimate result. In this group of cases of hypernephroma with metastases to bone, it has been difficult to follow many of the

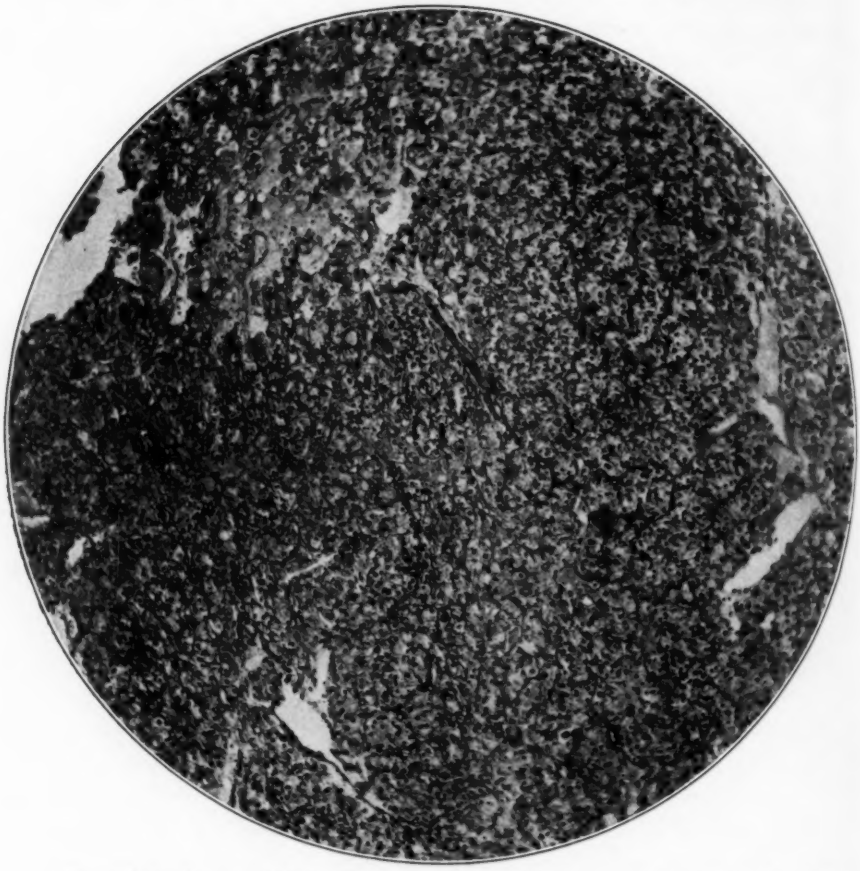

Fig. 25 (path. no. 29461).—Photomicrograph of the tumor shown in figure 24 Note the typical structure of hypernephroma cells with an occasional blood sinus. The cytoplasm of the cells is quite clear, and there is little evidence of stroma.

patients, but the data at hand point to the fact that irradiation alone offers as much for the prolongation of life as does surgical intervention alone or surgical measures combined with x-ray or radium therapy (table 4). One patient (path. no. 27964), who was treated by radium therapy, was living seventy-six months after the first symptoms of the tumor. Aside from the prolongation of life, however, there is

the problem of pain. Bloodgood has found in instances in which one metastatic lesion is present or in which a bone with multiple lesions is easily accessible to surgical measures, and in which the condition of the patient is such as to withstand the operation, that much relief from pain can be given by resection of the affected portion of the bone. One important factor in the treatment of this tumor by irradiation is the extremely resistant character of hypernephroma to low voltage radiation.[20] Unless roentgen therapy in keeping with that discussed under carcinoma of the breast is available, the patient should be referred elsewhere for treatment.

TUMORS OF MALE AND FEMALE GENITAL TRACT

Prostate.—Carcinoma of the prostate with metastases to bone is of frequent occurrence, as reported by those clinics and laboratories where considerable genito-urinary material is seen.[21] From among 1,020 cases of cancer of the prostate in the Brady Urological Institute and 20 cases registered by the Surgical Pathological Laboratory of the Johns Hopkins Hospital, 134 instances of metastases to the bone were found. It must be pointed out, however, that roentgenograms have been made in only about 50 per cent of the total number of cases, and in only 25 per cent of this number were secondary deposits in the bone found.

The bones most frequently involved are the pelvis and vertebrae, particularly the lumbosacral, more rarely the femurs and in two instances the lower end of the tibia and the skull.

The age incidence of the men is well beyond the age of 50 (table 6 *A*). These men showed obstructive urinary symptoms and enlargement of the prostate at the time the metastases were noted. In a personal communication with Dr. Waters and Dr. Hugh Young's clinic, I am informed that many patients following prostatectomy for extremely small carcinomas, which are actually found on subsequent pathologic examination of the prostate, develop osseous lesions a few years later.

The clinical course of these patients is one of progressive emaciation, secondary anemia and excruciating pains in the affected bones.

Roentgen Studies.—The usual x-ray picture of the bones invaded by the tumor is one of an osteoplastic nature. There is marked increase in formation of the bone, with areas of lighter mottling which suggest some destruction (fig. 26).

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20. Dresser, R.: Metastatic Manifestations of Hypernephroma in Bone, Am. J. Roentgenol. **13**:342, 1925.

21. Bumpus, H. C.: Roentgen Rays and Radium in the Diagnosis and Treatment of Carcinoma of the Prostate, Am. J. Roentgenol. **9**:269, 1922. Blumer, G.: A Report of Two Cases of Osteoplastic Carcinoma of the Prostate with a Review of the Literature, Bull. Johns Hopkins Hosp. **20**:200, 1909.

TABLE 6.—*Malignant Disease of the Male Genital Tract with Metastases to Bone*

A. Carcinoma of the Prostate

B.U.I.* No.	Race	Sex	Age	Location of Metastases	Symptoms Attending Appearance of Metastases	Treatment of Primary Tumor†	Roentgenogram	Duration of Primary Tumor Before Metastases, Mo.	Interval Between Primary Treatment and Metastases, Mo.	Result
19677	W	M	59	Right ischium	.....	X-rays, radium, March, 1930	Suggestive of metastases	24	26	
19568	W	M	78	Pelvis and spine	Pain	PP., May, 1913	Positive for metastases	12	..	Dead 23 days after operation
19523	W	M	59	Spine	.....	X-rays	Suggestive of metastases	72	..	
19453	W	M	62	Right ischium	.....	X-rays, radium, April, 1930	Positive for metastases	72	72	
19401	W	M	74	Spine and pelvis	.....	X-rays, radium, March, 1930	Positive for metastases	60	..	
19354	W	M	66	Sacrum	Pain	X-rays	Positive for metastases	6	..	
19264	W	M	70	Pelvis	Pain	X-rays	Positive for metastases	8	8	Dead
19238	W	M	70	Spine, pelvis	.....	X-rays	Positive for metastases	36	36	Dead ½ mo. later
19219	W	M	70	5th lumbar vertebra	Pain	.....	Probable metastases	24-36	2	Dead less than 1 mo. after observation
19158	W	M	61	Pelvis	.....	X-rays, radium, Jan., 1930	Positive for metastases	12	12	
19102	W	M	64	5th lumbar vertebra and ischium ilium	Pain	Punch operation, Dec., 1921	Positive for metastases	36	36	
18969	W	M	64	Pelvis and lumbar vertebra	Pain	.....	Positive for metastases	12	..	
18889	W	M	60	Ischium	Pain	X-rays	Positive for metastases	12	12	
18822	W	M	60	Lumbar spine	Pain	X-rays, radium, Aug., 1929	Positive for metastases	24	24	
18694	W	M	70	Pelvis, symphysis	.....	X-rays, radium, July, 1929	Positive for metastases	¾	..	
18591	W	M	70	Left ilium	Pain 12 mo. after onset; urinary symptoms	Radium	Suggestive of metastases	18	..	
18138	C	M	68	Sacrum, left ischium, right ilium	.....	P.P., Jan. 1929	Positive for metastases ?	4	..	
18119	W	M	66	Right ischium, left ilium	.....	Conservative P.P., Jan. 1929	Positive for metastases	24	..	
18085	W	M	..	Spine, pelvis	.....	X-rays, radium, Dec., 1928	Positive for metastases	22	..	
18017	W	M	59	Sacro-iliac region	Pain	Radium, x-rays, 1928	Positive for metastases	4	..	Alive 6 mo. after treatment
18014	W	M	50	Lumbar vertebra, symphysis pubis	Pain	Radium, Nov., 1928; x-rays	Suggestive of metastases	36-48	1	
17993	W	M	63	Vertebra, occiput, ribs (autopsy)	Headache?	Cystotomy, Nov., 1928	No roentgenogram; metastases found at autopsy	5	..	Dead following operation
17874	W	M	60	2d lumbar vertebra	.....	Radium, colostomy, 1929	Positive for metastases	6	..	
17841	W	M	64	Pelvis	Pain	P.P., Jan., 1930	Positive for metastases	12	..	
17836	W	M	50	Left ilium	.....	P.P., Oct., 1928	Suggestive of metastases	2	..	
17619	W	M	47	Seminal vesicle	Pain	Radium, April, 1927; x-rays	Positive for metastases	12	..	
17472	W	M	74	Left ilium	Pain	P.P., June, 1928	Suggestive of metastases	24	..	
17461	W	M	56	Spine, pelvis	.....	X-rays, conservative	Positive for metastases	24-36	24-36	
17397	W	M	53	Pelvis, sacrum	Pain	X-rays	Positive for metastases	48	48	
17391	W	M	66	Spine, pelvis	.....	X-rays, radium, June, 1928	Positive for metastases	27	27	

17381	W	M	67	4th lumbar vertebra	Pain	X-rays (no date given)	Suggestive of metastases	12	14	
17303	W	M	76	Spine, 4th and 5th lumbar vertebrae	.....	X-rays, conservative; P.P., April 1, 1928	Positive for metastases	3	4	
17195	W	M	65	Right ilium	.....	Radium, March, 1928	Suggestive of metastases	8	..	
17179	W	M	60	Spine, pelvis	.....	S.P., 1909; x-rays	Positive for metastases	..	..	
17168	W	M	85	Pelvis	.....	Radium, 1928	Positive for metastases	36	..	
16922	W	M	72	Pelvis, skull	Pain	P.P., Jan., 1928	Positive for metastases	13	..	
16802	W	M	62	Pelvis, spine	Pain	Radium, Dec., 1927; x-rays	Positive for metastases	8	..	
16765	W	M	62	Lumbar vertebra and pelvis	.....	Punch operation, Nov., 1927	Positive for metastases	1	..	
16499	C	M	80	Lumber vertebra and pelvis	.....	P.P., Sept., 1927	Positive for metastases	10	..	
16451	W	M	67	1st, 2d and 5th lumbar vertebrae	.....	P.P., conservative, Aug., 1927	Positive for metastases	12	15	Dead 16 mo. after operation
16419	W	M	60	2d lumbar vertebra	Pain	P.P., conservative, Aug. 1927; x-rays, Oct., 1927	Positive for metastases	6	..	
16232	W	M	57	Symphysis pubis	.....	Excision of tumor, March, 1927; postoperative radium and conservative P.P., July, 1927	Positive for metastases	9	14	Alive and well over 2 yr. after second operation
16091	W	M	55	Lumbar vertebra	Pain	P.P., conservative, June, 1927; x-rays	Positive for metastases	12	..	
16027	W	M	55	Right ilium, ischium, 5th lumbar vertebra	Pain	P.P., Aug., 1927; x-rays and radium, 2 years before	Positive for metastases	24	..	
15832	W	M	63	Lumbar vertebra and ilia	.....	X-rays, radium, May, 1928	Positive for metastases	12	10	
15794	W	M	71	5th lumbar vertebra, sacrum, right ilium	.....	P.P., April, 1927; radium	Suggestive of metastases	60	..	
15791	W	M	70	Lumbar vertebra, sacrum	Pain	X-rays, radium, March, 1927	Suggestive of metastases	12	6	Dead 1 mo. after treatment
15761	W	M	56	Pelvis, sacrum, coccyx	Pain	P.P., March, 1927	Strongly suggestive of metastases	24	12	
15647	W	M	61	Ilium, ischium, pubis	Sciatic pain	P.P., March, 1927	Positive for metastases	60-96	..	
15529	W	M	72	Pelvis	Pain	Radium, x-rays, 1926	Positive for metastases	36	..	
15504	W	M	66	Ischium, sacrum, lumbar spine	Pain	X-rays, Feb., 1927	Positive for metastases	7	..	
15476	W	M	82	Spine, pelvis	Pain	P.P., Dec., 1926; x-rays	Positive for metastases	4	..	
15470	W	M	75	Symphysis pubis	.....	P.P., conservative, Oct., 1926	Positive for metastases	8	..	
15371	W	M	80	4th lumbar vertebra, sacrum, ilium	.....	.....	Suggestive of metastases	48	..	Dead
15357	W	M	63	Pelvis	.....	P.P., May, 1926	Positive for metastases	24	..	
15346	W	M	..	Pelvis	Pain	P.P., conservative, Nov., 1926	Suggestive of metastases	36	..	
15275	W	M	..	Pelvis	.....	P.P., Sept., 1926	Positive for metastases	12	..	
15241	W	M	..	Spine, pelvis	.....	P.P., Oct. 1926	Positive for metastases	18	..	Dead 1 mo. after operation
15154	W	M	66	Spine, pelvis, right and left ischia	.....	Radium advised	Positive for metastases	1	..	
14614	W	M	71	Sacrum, 5th lumbar vertebra	Pain	P.P., April, 1926	Suggestive of metastases	9	..	
14508	W	M	68	Sacro-iliac region	.....	Radium, April, 1926	Probable metastases	18	24	
14485	W	M	46	Right ilium	.....	P.P., conservative, April, 1926	Suggestive of metastases	22	14	
14413	W	M	61	Pelvis	.....	Radium, x-ray, Feb., 1926	Positive for metastases	24	..	
14423	W	M	69	Sacrum, ilium, right ischium	.....	X-rays, Dec., 1925	Positive for metastases	18	..	

* Brady Urological Institute.
† In this column P.P. indicates perineal prostatectomy; S.P., suprapubic prostatectomy.

TABLE 6.—*Malignant Disease of the Male Genital Tract with Metastases to Bone—Continued*

B.U.I. No.	Race	Sex	Age	Location of Metastases	Symptoms Attending Appearance of Metastases	Treatment of Primary Tumor	Roentgenogram	Duration of Primary Tumor Before Metastases, Mo.	Interval Between Primary Treatment and Metastases, Mo.	Result
14192	W	M	..	Sacrum, ilia	.....	.....	Positive for metastases	36	..	
14149	W	M	65	Left ilium, symphysis pubis, sacrum	Pain	P.P., 1922	Very suggestive of metastases	25	18	
13936	W	M	74	Ischium, right pubis, 2d lumbar vert.	Pain	Radium, x-rays, Sept., 1925	Positive for metastases	12	..	
13913	W	M	78	Sacrum, ilium, pubes	.....	Radium	Positive for metastases	6	..	
13767	W	M	69	Sacrum, ilium, lower lumbar vertebae	Pain	X-rays, Sept., 1924; radium July, 1925	Positive for metastases	24	..	
13625	W	M	77	Ilia	.....	Radium, July, 1925	Positive for metastases	48	..	
13471	W	M	56	5th lumbar vertebra, sacrum, ilium, left pubis	Pain	Cystotomy, Nov., 1924	Very suggestive of metastases	12	..	
13466	W	M	72	Pelvis	Pain	.....	Positive for metastases	24	..	Dead few mo. later
13394	W	M	52	Right ischium	Pain	Radium, April, 1925	Positive for metastases	15	..	
13356	..	M	..	Pelvis, upper end of right femur	.....	.....	Positive for metastases	..	..	
13317	W	M	78	Pelvis, sacrum	.....	.....	Positive for metastases	21	..	Dead before treatment was begun
13311	W	M	77	Pelvis	.....	P.P., March, 1925	Suggestive of metastases	24	..	Dead from operation
12993	W	M	57	Pelvis	Pain	.....	Positive for metastases	..	..	
12757	W	M	75	Right ilium	.....	Radium, Sept., 1924	Probable metastases	3	1	
12859	W	M	74	Pelvis, lumbar vertebra	Pain	X-rays, radium, Oct., 1924	Positive for metastases	9	..	
12580	W	M	68	5th lumbar vertebra	Pain	X-rays, radium, March, 1924; P.P., Jan., 1925	Beginning metastases	..	..	
12553	W	M	64	Right ilium	.....	X-rays	Positive for metastases	9	..	
12544	W	M	66	Ischium, right pubis	Pathologic fracture	P.P., June, 1924; postoperative x-rays	Positive for metastases	12	..	
12495	W	M	64	Spine, pelvis, sacrum	Pain	Radium, June, 1924	Positive for metastases	108	..	
12488	C	M	57	Pelvis, lower lumbar vertebrae	Pain	X-rays, radium, Jan., 1924; P.P., July, 1924	Positive for metastases	24-36	..	
12459	W	M	63	Spine, pelvis	Pain	X-rays, radium, advised	Positive for metastases	6	..	
12275	W	M	70	Pelvis	.....	P.P., May, 1924	Positive for metastases	60	..	
12257	W	M	58	Spine, pelvis	Stiffness of hip	S.P., May, 1923; x-rays and radium	Positive for metastases	48	..	Dead 15 mo. after operation
12084	W	M	60	Symphysis pubis, left femur, right ilium	.....	Punch operation and radium, Feb., 1924; conservative P.P., March, 1924	Suggestive of metastases	12	2	
12060	W	M	63	Lumbar vertebrae, sacrum, ribs	Pain	P.P., radium, Feb., 1924	Positive for metastases	9	..	
12035	W	M	56	.....	Pain	X-rays, 1925	Sclerosis of vertebrae and bones of pelvis; no definite metastases	..	..	

11901	W	M	58	Sacrum, ilia	Pain	X-rays, Nov., 1923	Positive for metastases	5	..	
11882	W	M	58	3d lumbar vertebra, sacrum, ilia	Pain	Radium, x-rays, 1921-1923	Positive for metastases	24	..	
11825	W	M	68	5th lumbar vertebra, right ilium, pubes, sacrum	Pain	.....	Positive for metastases	6	..	
11778	W	M	63	Pelvis, spine, 4th and 5th lumbar vertebrae	Paraplegia	S.P., 1923	Positive for metastases	6	..	Dead (?)
11650	W	M	66	Sacro-iliac region, right	.....	X-rays, Aug., 1923	Positive for metastases	..	..	
11575	W	M	63	Pelvis, sacrum	Pain	Radium, July, 1923	Suggestive of metastases	12	..	Dead 3 weeks after treatment
11552	W	M	74	Sacrum, pelvis	.....	Radium, July, 1923	Positive for metastases	36	..	
11467	W	M	63	Sacrum, spine	Pain	Radium, June, 1923	Positive for metastases	36-48	..	
11419	W	M	57	Pelvis, lower lumbar vertebrae	Pain	Radium, June, 1923	Positive for metastases	60	2	
11338	W	M	69	Spine, pelvis, sacrum	Pain	Radium, April, 1923; x-rays, May, 1923	Positive for metastases	12	..	
11244	W	M	48	Spine, pelvis	Pain	P.P., x-rays, March, 1923	Suggestive of metastases	4	..	
10938	W	M	75	Ribs, vertebrae	Pain	Punch operation after radium and x-rays, Dec., 1924	X-ray negative; autopsy findings: extensive metastases	24	24	Dead 2 mo. after appearance of metastases
10919	W	M	75	Sacrum	.....	Radium, Nov., 1922	Positive for metastases	24	..	Living 2½ yr. later
10776	W	M	64	Right ilium	Pain	P.P., conservative; radium, Sept., 1922	Positive for metastases	12	9	
10657	W	M	59	Spine, pelvis, sacrum	Pain	Radium, July, 1922; x-rays	Positive for metastases	1¼	..	
10562	W	M	75	Femora, pelvis, spine, humerus, clavicles, scapulae	Pain	S.P.,, x-rays, radium, 1922 (June–July)	Positive for metastases	36	..	Dead 4 mo. after x-ray treatment
10517	W	M	76	Pelvis	.....	Radium, June, 1922	Suggestive of metastases	2	..	Dead
10495	W	M	70	Symphysis pubis, right hip	Pain	P.P., March, 1922; radium, March, 1922	Positive for metastases	12	..	
10491	F	M	67	Sacrum, ilia, 11th dorsal vertebra	.....	P.P., radium, May, 1922	Positive for metastases	12	..	Dead 7 mo. after operation
10478	W	M	71	Sacrum, pelvis	.....	P.P., May, 1922; radium, May, 1922	Positive for metastases	18	..	Dead 11 mo. after operation
10400	W	M	75	Lower lumbar vertebrae	.....	P.P., Feb., 1922, radium 2 weeks later (S.P., 10 months before)	Positive for metastases	..	..	
10391	W	M	76	Spine	.....	P.P., April, 1922	Suggestive of metastases	1	..	
10055	W	M	59	4th and 5th lumbar vertebrae	Pain	Radium, Nov., 1921	Positive for metastases	15	..	
9958	W	M	78	4th and 5th lumbar vertebrae, pelvis	Pain	Radium	Positive for metastases	2½	..	
9493	W	M	64	Left ilium, sacrum	Pain	P.P., March, 1921	Positive for metastases	60	33	
9300	W	M	53	Sacrum	.....	Radium and x-rays	Suggestive of metastases	36	..	
9018	W	M	68	Spine, pelvis	Pain	P.P., Oct., 1920	.....	40	4	
8493	W	M	62	Pelvis	Pain	Radium, Feb.-March, 1920	Positive for metastases	..	..	Dead 6 mo. after initiation of treatment
8372	W	M	70	Spine, hips	Pain	P.P., Dec., 1919; radium, Jan., 1920; x-rays	Positive for metastases	42	6	Dead 15 mo. after appearance of metastases
8234	W	M	62	Spine, pelvis	.....	P.P., Dec., 1919	Positive for metastases	132	54	Dead 2½ yr. after appearance of metastases
7272	W	M	69	.....	Pain	P.P., Nov., 1918	Negative for metastases	..	..	Dead 1 yr. after operation

TABLE 6.—*Malignant Disease of the Male Genital Tract with Metastases to Bone—Continued*

B.U.I. No.	Race	Sex	Age	Location of Metastases	Symptoms Attending Appearance of Metastases	Treatment of Primary Tumor	Roentgenogram	Duration of Primary Tumor Before Metastases, Mo.	Interval Between Primary Treatment and Metastases, Mo.	Result
7240	W	M	61	Sacrum, coccyx	Pain	.....	Positive for metastases	..	..	
6838	W	M	66	Sacrum	Pain	P.P., 1918	Strongly suggestive of metastases	36	..	Dead 1½ yr. after operation
6745	W	M	71	4th and 5th lumbar vertebrae, sacrum, ilia	Pain, 3 yr.; incontinence of urine and feces	P.P., 1918; radium	Positive for metastases	..	..	
6408	W	M	79	Lumbar vertebrae	.....	.....	Suggestive of metastases	..	..	
4417	W	M	68	Lumber vertebrae, and pelvis	.....	S.P., 1915; radium and x-rays	Positive for metastases	144	108	Dead 9 yr. after operation
2131	W	M	57	5th lumbar vertebra, sacrum, ilium	Pain	P.P., 1909; punch operation, 1924; excision, 1927	Positive for metastases	120	..	
				Cases From the Files of the Surgical Pathological Laboratory						
42182	W	M	55	Pelvis	.....	S.P., May, 1929	Positive for metastases	24	..	
33307	W	M	68	Pelvis	.....	X-rays, 1923	Positive for metastases	..	..	Dead few months after treatment
18375	W	M	57	Lower end of femur	Pathologic fracture	Amputation of leg, metastases, Oct., 1915	Positive for metastases	6	..	Dead following operation
10341	W	M	54	Upper third of femur	Pain, pathologic fracture	.....	Positive for metastases	..	..	Dead a few days after observation
1643	W	M	75	Tibia, shaft	Swelling	Amputation of thigh (metastatic growth), Jan., 1897	.....	10	3	Dead 8 mo. after operation

B. Testicular Malignant Disease

Path. No.	Race	Sex	Age	Primary Tumor	Location of Metastases	Symptoms Attending Appearance of Metastases	Treatment of Primary Tumor	Roentgenogram	Treatment of Metastases	Duration of Primary Tumor Before Metastases, Mo.	Interval Between Primary Treatment and Metastases, Mo.	Result
42856	W	M	56	Sarcoma of testicle	Skull, frontal bone	Tumor	Excision of right testicle, April, 1930	Positive for metastases	X-ray, April, 1930	8	Duration of metastatic growth 10 mo.	Dead 3 mo. after operation
29669	W	M	40	Carcinoma of testicle	Ribs, 4th and 5th	Pain	Orchidectomy, Feb., 1922; postoperative radium	Positive for metastases	Radium, x-ray, March, 1922	2	Metastases observed in x-ray 3 mo. before symptoms of primary tumor	Well 3 yr., 9 mo. after operation

* Duration of metastasic growth.

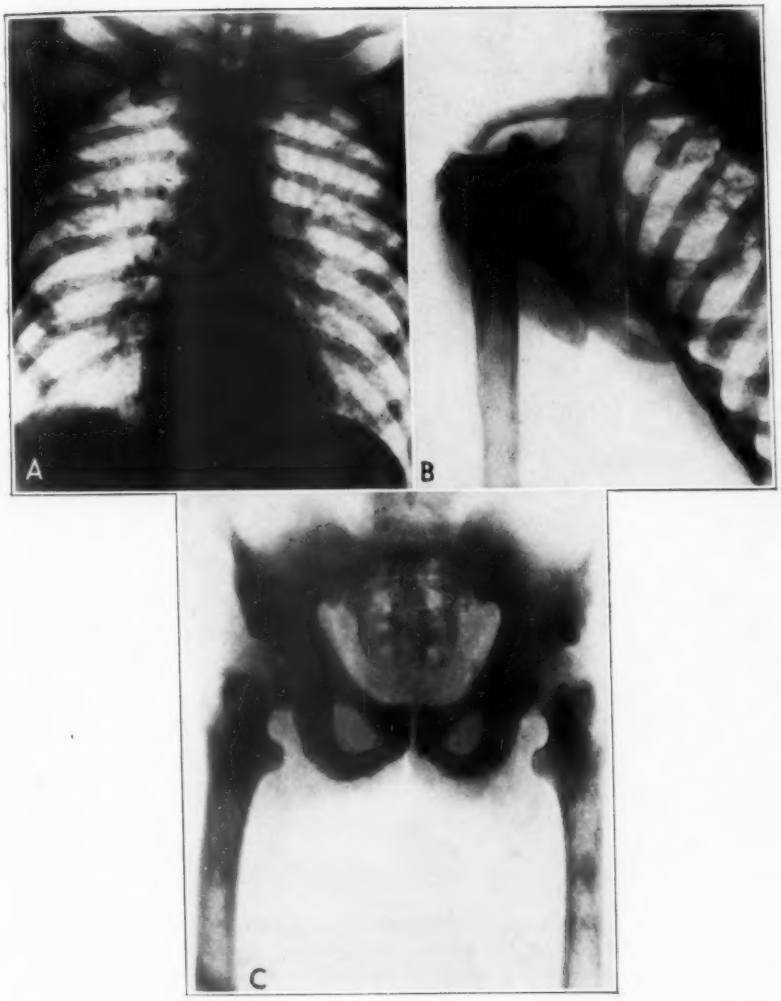

Fig. 26 (path. no. 42182).—Osteoplastic nature of bony metastases from carcinoma of the prostate as depicted in the roentgenogram. *A* shows involvement of the ribs and clavicle with some bony destruction and formation of new bone. *B*, the upper end of the humerus with marked sclerosing reaction in the region of the head from tumor invasion. *C*, shows multiple involvement of the entire pelvis and associated involvement in the upper part of both femurs. Note again the marked production of bone in the affected areas.

Simpson [22] has reported a case in which there was no clinical roentgenographic or gross anatomic evidence of vertebral metastases, which on subsequent microscopic study, revealed generalized medullary carcinoma of the prostate gland.

Bumpus,[23] in a study of 362 cases at the Mayo Clinic, found that the osteoplastic type of bony metastases was by far the more common, but that osteoclastic changes did occur in a few of the cases.

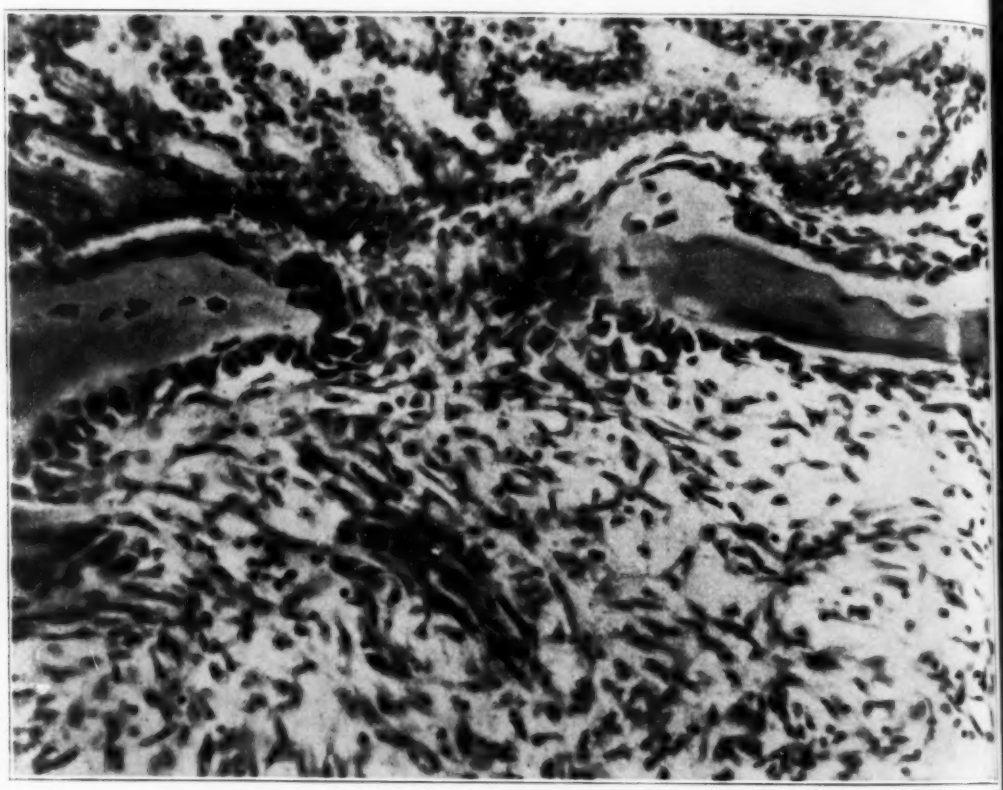

Fig. 27 (path. no. 1643).—Photomicrograph showing definite glandular structure of the invading prostatic cancer, while about this tumor tissue reactive bone can be seen which is an attempt on the part of the osseous structure to wall off the advance of the tumor.

On gross examination, these metastatic areas are usually white or grayish nodules with many newly-formed trabeculae of bone as well

22. Simpson, W. M.: Diffuse Vertebral Metastasis of Prostatic Carcinoma Without Bony Changes, Am. J. Roentgenol. **15**:534, 1926.

23. Bumpus, H. C., Jr.: Carcinoma of the Prostate, Surg. Gynec. & Obst. **32**: 31, 1921.

as spicules of old bone undergoing absorption by direct contact with the tumor cells. The prostatic glandular structure can be made out in many of the secondary deposits in bone. About this tumor tissue is found much reactive bone, which is an attempt on the part of the osseous structure to wall off the disease invading its substance (fig. 27).

The reaction of bone to prostatic carcinoma is quite the reverse of that usually seen in other metastatic lesions, except where osteoclastic invasion by tumor has been treated by roentgen therapy. Many possibilities arise in connection with this phenomenon. The most tenable one, however, is that the invasive powers of the metastatic tumor are so moderate that proliferation of the bone can keep pace with the invasion by tumor. The validity of this statement becomes more apparent when one considers the reaction of tumor deposits from other primary lesions to roentgen therapy.

Roentgen therapy offers some relief from pain but is not effective in eradicating the lesion or in greatly prolonging the life of the patient. Resection of the affected bone or amputation of the diseased limb has in some instances made the patient more comfortable for the time he had to live.

Testicle.—Malignant disease of the testicle with metastases to bone is of rare occurrence. Of thirteen cases in which the diagnosis was carcinoma, in only one instance is there a record of metastases (table 6 *B*).

A man, aged 40 (path. no. 29669), had orchitis of the left testicle with subsequent atrophy at the age of 18, after an attack of measles. For two months prior to admission to the hospital twenty-two years later, he had noted a swelling in the testicle. On examination, it was found to be a hard, irregular mass. There was no enlargement of the regional lymph glands and no palpable mass in the abdomen. The blood and urine were normal. On roentgen examination of the various bones, the fourth and fifth ribs showed destruction. The patient had noted some pain in the region of these lesions for over a year. Just prior to admission, there had been a noticeable loss of weight. Following roentgen therapy both over the testicle and the affected ribs, orchectomy was performed, and uneventful recovery followed. In 1922, the patient had remained well twenty-eight months with recalcification of the fourth and fifth ribs. Since that time, the patient has been lost from observation.

In forty-two cases of sarcoma of the testicle registered in the Surgical Pathological Laboratory, there is only one instance of metastases to the bone (table 6 *B*, path. no. 42856).

A white man, aged 56, presented himself with a growth on his forehead of eleven months' duration. When first noticed, it was the size of the index finger. There had been no pain or headache. A swelling of the right testicle had been noticed for at least a year and a half which followed a slight injury. Six months prior to his admission to the hospital, the swelling suddenly disappeared with

subsequent fluctuations in size. Seven weeks before, the patient had what he called an attack of influenza, with a temperature of 102 F. Following this, a physician was interviewed who gave the patient serum treatment for the tumors, which was followed again by an elevation of temperature. On examination, the tumor in the forehead was found to be the size of a small orange and extended from the nose to the hair line. There was fluctuation in the tumor.

The x-ray picture revealed destruction of the frontal bone, particularly of the outer table, immediately above the frontal sinuses with infiltration and swelling of the overlying soft structures. There was no evidence of metastases in the other

TABLE 7.—*Maglinant Disease of the Female Genito-Urinary with Metastases to Bone*

Path. No.	Color	Sex	Age	Primary Tumor	Location of Metastases	Pathologic Fracture	Treatment of Metastases	Duration of Metastases
				Carcinoma of the Female Genital Tract				
40714	W	F	53	Carcinoma of uterus	Right femur, right pelvis	.....	.....	.....
3779	W	F	35	Carcinoma of uterus	Right ilium	.....	Exploration, drainage	Lived 10 mo.
3429	C	F	49	Carcinoma of uterus	Right pelvis (ilium)	.....	.....	Lived 4 mo.
36552	W	F	60	Carcinoma of cervix	Right humerus, right side of skull, upper third of femur	.....	.....	.....
20111	W	F	38	Carcinoma of cervix	Ilium	.....	.....	.....
27170	W	F	47	Carcinoma of ovary	Metacarpal, right foot	.....	.....	.....
				Carcinoma of the Bladder				
11970	W	F	50	Carcinoma of bladder	Tibia, right	.....	Resection of tibia	.....
				Sarcoma of the Female Genital Tract				
29529	W	F	14	Sarcoma of ovary	Skull, lower third of left femur, upper end of femur, left ilium	.....	X-rays	Lived 13 mo.

bones of the skeleton. The testicle was removed by Dr. Bloodgood, and the patient was given roentgen therapy, with rapid disappearance of the tumor in the forehead, which was soon followed, however, by vomiting and other systemic disturbances. There was never severe anemia or emaciation. The patient died three months after operation, having lived fourteen months from the first sign of the metastases.

Bladder.—One example of carcinoma of the bladder with metastases to bone (table 7, path. no. 11970) is recorded.

A white woman, 50 years old, six weeks before admission to the hospital felt pain in the inner portion of the right tibia on walking. This was followed by swelling of the right foot. The pain was worse at night, and marked swelling developed in the midshaft of the tibia. On roentgen examination, there was

evidence of destruction of the bone beneath the periosteum on the side toward the fibula, with slight evidence of formation of new bone, characteristic of metastatic cancer. Resection of the tibia was performed, and microscopic examination revealed tissue of the transitional type resembling that seen in tumors of the bladder.

Following the operation, hematuria developed, and after two months and nine days a cystoscopic examination was done which showed a tumor of the bladder in the region of the trigone. Unfortunately, the patient was lost from observation soon after recovery from operation, so that the ultimate progress of the disease could not be ascertained.

Uterus.—From among eighty-six cases with carcinoma of the uterus, five cases (5.6 per cent) showed metastases to bone (table 7), two of these patients having the primary lesion located in the cervix. The age incidence in these cases extended from 35 to 60 years. The metastases were found four times in the pelvis, twice in the femur and once in the humerus, skull and metacarpals of the right foot.

Clinically, varying degrees of pain with disturbances of use in the affected extremities were common symptoms. At times an associated swelling was noted in the glands of the groin and of the affected limb.

Owing to the fact that uterine carcinoma as a whole invades lymph nodes relatively late, Ewing [24] has found a striking tendency of the disease to remain localized either to the uterus or to its immediate vicinity. As a rule, tumors of the fundus long remain confined by the muscular wall. This is not the case in cervical carcinoma, which invades the parametrium early. The duration and type of the disease undoubtedly influences the rapidity of the extension.

The clinical course of the advancing disease is dominated by secondary invasion of surrounding organs, many cases terminating through uremia from occlusion of the ureters. Characteristic cachexia develops in most cases, but nutrition may remain surprisingly good.

The x-ray picture shows destruction of the bone (fig. 28). There is little tendency to formation of bone, and there is nothing typical of the lesion to set it apart from the other osteoclastic types of metastases.

In this group of cases there is little to offer with regard to treatment except the general principles that have been laid down in the preceding pages. Ford [25] recently showed that there is a slightly smaller percentage of cases showing distant metastases, including metastases to the bone, following adequate irradiation of the primary lesion than in those cases in which radium therapy is not employed. Some relief from pain

24. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 601.

25. Ford, F. A.: Distant Metastases in Carcinoma of the Cervix of the Uterus, Minnesota Med. **13**:489 (July) 1930.

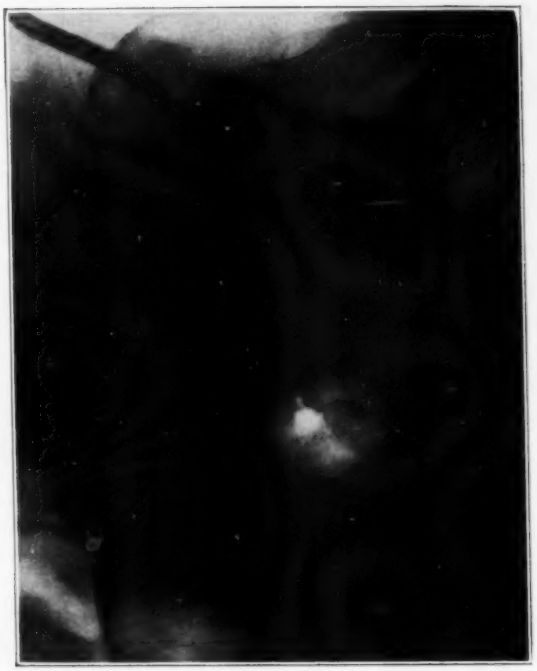

Fig. 28.—Roentgenogram of the pelvic bones showing invasion of the ilium by extension of tumor from the uterus.

Fig. 29 (path. no. 29529).—Roentgenogram depicting invasion of the tumor at the lower end of a femur from an ovarian sarcoma. Note the destruction of the bone and subperiosteal involvement on the posterior aspect of the bone.

in the osseous lesions is obtained by irradiation, but this is more transient than the relief following the irradiation of mammary carcinomatous metastases to bone.

Ovary.—There are two instances, 2.8 per cent, of ovarian tumor with metastases to bone among sixty-nine such cases in this laboratory (table 7).

One of these patients was a woman, aged 47 (path. no. 27170), in whom, four months prior to admission, sudden pain developed over the entire abdomen, and lasted for a few days. The abdomen soon became filled with fluid; a subsequent laparotomy was performed, and bloody fluid was found. The right ovary was much enlarged. The patient made an uneventful recovery and returned home. Twelve months ago, she began to limp because of discomfort in the right foot. A roentgenogram of the foot showed destruction at the proximal end of the third metatarsal bone. Roentgen therapy was administered, and the condition of the foot improved. The patient has been lost from observation.

The other case (path. no. 29529) was that of a young girl, aged 14, who first noticed pain in the left knee with limp, and pains in the abdomen with some diarrhea. Eight months later, a lump appeared on the posterior portion of the skull. A laparotomy was subsequently done for pain in the abdomen, free fluid was found, and a small tumor of the right ovary was removed and was diagnosed sarcoma (mesothelioma).

Roentgen therapy was instituted, and though some relief from pain followed, the course was progressively downward. The patient died twenty months after the first symptoms of metastases. Roentgen examination revealed areas of destruction in the skull and in the lower third and the upper end of the femur (fig. 29) and in the left ilium.

MALIGNANT DISEASE OF THE THYROID

In those reports that deal with a large series of cases of malignant disease of the thyroid, metastases to bone are of frequent occurrence. Ehrhardt [26] found bones affected in 66 of 238 cases of carcinoma of the thyroid, and Ewing [27] is of the opinion that in malignant conditions of the thyroid the bones are involved only less frequently than in cases of mammary and prostatic cancer, giving the following order of frequency in bones affected: skull, sternum, spine, ribs, humerus, femur and pelvis. The metastatic growths appear near the epiphyses either as central (fig. 30) or subperiosteal lesions. Much has been written concerning the so-called metastatic tendencies of the "benign metastasizing goiters." Simpson [28] reported three cases in which the

27. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 955.

28. Simpson, W. M.: Three Cases of Thyroid Metastasis to Bones, Surg. Gynec. & Obst. **42**:489, 1926.

TABLE 8.—*Malignant Condition of the Thyroid with Metastases to Bone*

Path. No.	Color	Sex	Age	Primary Tumor	Location of Metastases	Pathologic Fracture	Treatment of Metastases	Duration of Metastases
40950	W	F	51	Carcinoma of thyroid	Upper end of left humerus	.....	Exploration	.....
40892	..	M	56	Sarcoma of thyroid	Bone	.....	X-rays	Lived 16 mo.
37300	W	F	55	Carcinoma of thyroid	Skull	.....	.....	.....
31358	W	M	70	Carcinoma of thyroid	Ribs and sternum, right 6th 7th and 8th ribs	.....	.....	Lived 24 mo.
28366	W	M	45	Carcinoma of thyroid	Neck of femur	Femur	Curetting of tumor	.....
26823	W	F	54	Carcinoma of thyroid	Upped third of right humerus, right clavicle	Right clavicle	Erysipelas and prodigiosus toxins (Coley's), radium, amputation and x-rays	Lived 24 mo.

Fig. 30 (path. no. 26823).—Roentgenogram depicting involvement of the bone in the upper end of a humerus. Note the marked destruction and expansion in the region of the nutrient vessels. There is also evidence of diffuse involvement of the lower portion of the shaft without distortion.

microscopic picture of the tissue removed from osseous deposits was that of typical thyroid tissue with the patients apparently presenting clinically benign goiters, but on careful observation of the clinical course and subsequent pathologic changes, these cases were found to show malignant degeneration in the thyroid gland. This, together with evidence which he accumulated, points to the fact that many such cases show some existent malignant change in the thyroid gland.

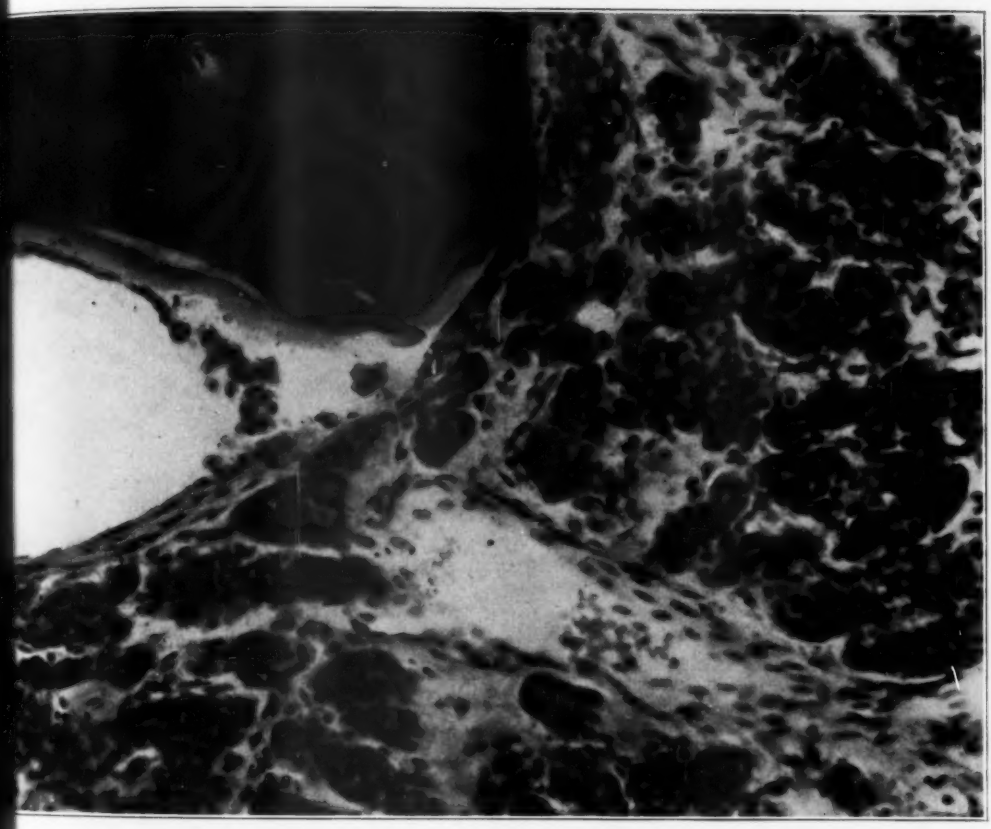

Fig. 31 (path. no. 26823).—Microscopic picture showing marked proliferation of tumor cells, with a spicule of old bone being destroyed by direct contact with the tumor cells.

In the six cases of malignant disease in the thyroid gland, with metastases to bone (table 8) recorded here, the ages ranged beyond 40 and well into late life. The cases were equally divided between the sexes.

There are too few cases to draw any conclusion concerning the incidence of involvement of the bone, but the evidence points to both a lymphatic and a hematogenous type of invasion.

The clinical course in these cases was usually one of progressive emaciation with symptoms referable to the bones that were the seat of the metastases. Pulmonary symptoms where the gland had invaded the structure of the neck and mediastinum causing pressure were marked in some cases.

Roentgen therapy was used in one instance, and in another erysipelas and prodigiosus toxins (Coley), radium therapy, subsequent amputation and roentgen therapy were combined, but despite the alleviation of pain the course of the disease proved fatal within two years.

The microscopic picture shows marked proliferation of tumor cells with little or no attempt at bone repair. Spicules of old bone are destroyed by direct contact with the tumor cells (fig. 31).

MALIGNANT DISEASE OF THE GASTRO-INTESTINAL TRACT

Stomach.—The literature related to carcinoma of the stomach and its subsequent metastases to bone is limited. Moore,[29] of the Mayo Clinic, up to 1919 had not observed a single metastatic lesion to bone from cancer of the stomach. Kaufmann[30] reported 2.5 per cent of metastases to bone in a review of 309 cases of malignant disease of the stomach. Schlesingers[30] found an incidence of 9.3 per cent in 54 cases, and Jenkinson,[31] in reviewing the literature, could find only 32 cases in which carcinoma of the stomach had metastasized to bone.

From a series of 537 patients who were found to have carcinoma of the stomach, registered in this laboratory, only 7, or 1.03 per cent, were subsequently found to be affected by metastases to bone (table 9). The ages of these patients ranged between 32 and 71. The bones involved were, in the order of frequency: ribs, 4 cases; pelvis and femur, 3 cases; vertebrae, 2 cases; sternum, skull and scapula, 1 each.

The frequent involvement of the ribs without metastases to the lung points to a lymphatic route of dissemination, while the mode of invasion in more distant bones is open to question.

In one instance (path. no. 39012), a pathologic fracture was found at the lower third of the right femur.

Most of the metastatic lesions in this group were examined at autopsy, but in two instances in which roentgen examinations were recorded (figs. 32 and 33), either diffuse mottling with destruction of bone and no distortion of the bone shell was present, or a slight expansion accompanied the central cystic lesion.

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29. Moore (footnote 1, second reference).

30. Quoted by Jenkinson.

31. Jenkinson, E. L.: Primary Carcinoma of the Gastro-Intestinal Tract Accompanied by Bone Metastasis, Am. J. Roentgenol. **11**:411 (May) 1924.

The clinical course is well illustrated in the following case report (path. no. 43240):

A white man, aged 40, was admitted to the hospital complaining of an inability to walk, with pain in the legs and in the back of the neck. He had previously suffered for nine months with a sensation of pins and needles in the feet on walking. His feet felt cold, and the skin was exceedingly dry over these extremities. Seven months prior to admission, he had fallen on his back, and severe pain had followed for several days. Four months later, a progressive weakness of the legs was noted and finally an inability to walk. Occasionally he had suffered from attacks of vomiting, and there was constant headache.

TABLE 9.—*Carcinoma of the Stomach with Metastases to Bone*

Path. No.	Color	Sex	Age	Primary Tumor	Location of Metastases	Pathologic Fracture	Treatment of Metastases	Duration of Metastases
44477	W	F	54	Carcinoma of stomach	Sternum, vertebra, femur, ribs, pelvis	.....	.....	.....
43246	C	M	32	Carcinoma of stomach	Bones	.....	.....	.....
43244	W	F	70	Carcinoma of stomach	5th left rib	.....	.....	.....
43242	W	M	39	Carcinoma of stomach	Right 4th, 5th and 6th ribs, left 4th, 5th and 9th ribs, 1st lumbar vertebra, 1st and 10th thoracic vertebrae, left parietal bone	.....	.....	.....
43240	W	M	40	Carcinoma of stomach	Right femur and ilium, 2d and 5th right ribs	.....	Rest in bed	Lived 9 mo.
38012	W	M	59	Carcinoma of stomach	Lower third of right femur, left ilium, right acetabulum	Femur	.....	Lived 24 mo. plus
36342	W	M	71	Carcinoma of stomach	Left scapula	.....	X-rays	Lived 14 mo.

On examination, the patient was found to be quite emaciated, and he was unable to sit up in bed; the knee jerks and deep reflexes elsewhere were absent. There was a fulness over the outside of the crest of the right ilium and a distinct thickening of the head of the femur. The blood showed a moderate secondary anemia, which gradually became more severe. The ultimate clinical course was progressively downward, and the patient died nine months after the first symptoms of metastases.

An interesting feature of the blood in cases of metastases of the bone from carcinoma of the stomach is reported by Piney [7] and others.[32]

32. Parmentier, E., and Chabrol, E.: Anémie grave et métastases cancéreuses dans la moelle des os, Bull. et mém. Soc. méd. d. hôp. de Paris **28**:341, 1909. Schleip, K.: Zur Diagnose von Knochenmarkstumoren aus dem Blutbefunde, Ztschr. f. klin. Med. **59**:261, 1906. Harrington, A. W., and Kennedy, A. M.: Bone Marrow Metastases and Anemia in Gastric Carcinoma, Lancet **1**:378, 1913.

Fig. 32 (path. no. 36342).—Roentgenogram showing diffuse mottling with destruction of the bone in the head of a humerus and in the adjoining scapula from carcinoma of the stomach.

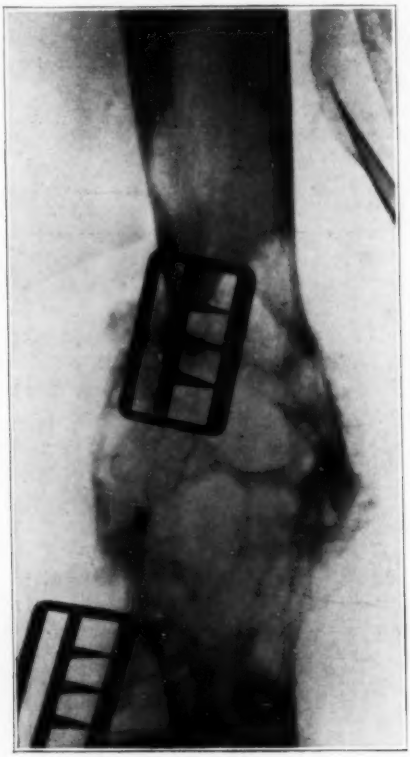

Fig. 33 (path. no. 39012).—Roentgenogram showing diffuse cystic destruction in the lower shaft of a femur from carcinoma of the stomach metastasizing to the bone. In the shaft above the area of destruction the cortex is seen to be eroded from within.

Changes in the blood of a pseudopernicious type were found in these cases, and are recorded in only one other type of metastatic tumor—carcinoma of the breast metastasizing to bone. This is in contrast to the ordinary type of secondary anemia usually seen. In one case of the present series (path. no 44477), a similar condition was noted in the blood.

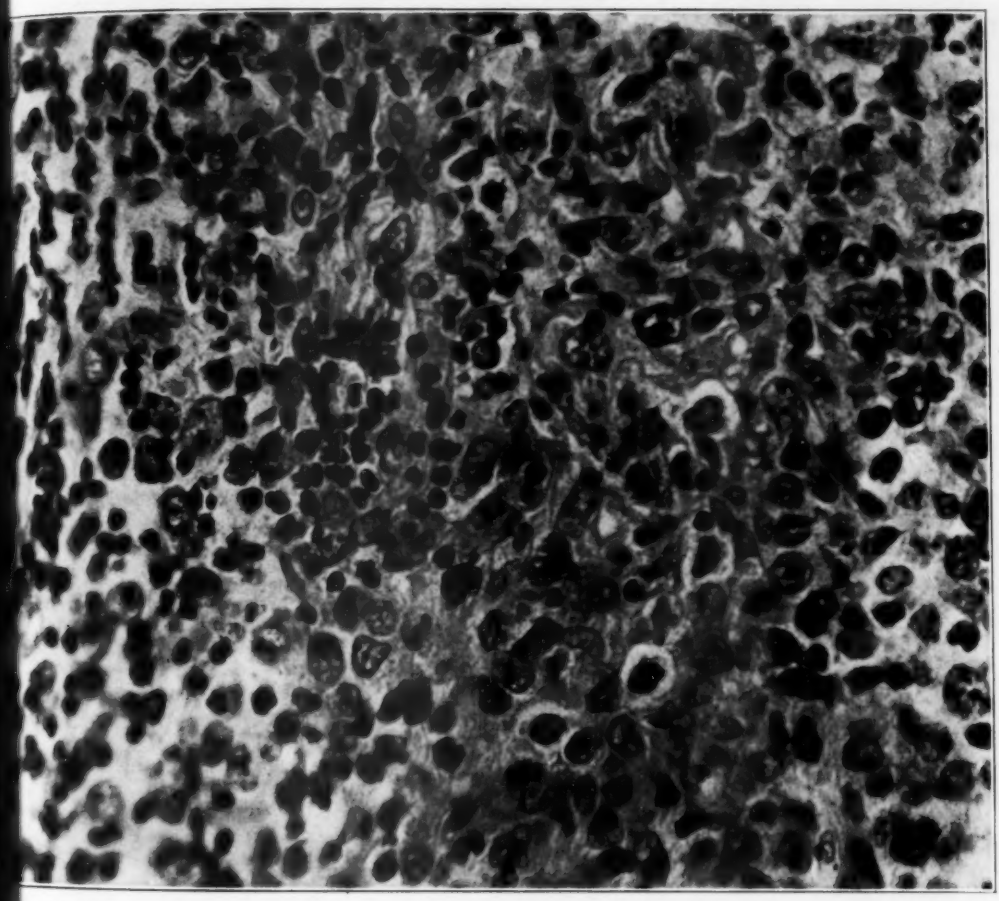

Fig. 34 (path. no. 44477).—Photomicrograph showing invasion of a lymph gland by tumor tissue from medullary carcinoma of the stomach.

A white woman, aged 54, had always been healthy until three years before admission to the hospital, when she became quite weak and pale, and began losing weight.

Six months before admission to the hospital she noticed enlargement of all the lymph nodes and a progressive downhill course with fever and sweats. The blood

on admission revealed 3,100,000 red blood cells, 10,600 white blood cells, 340,000 platelets with 30 per cent of polymorphonuclear cells, 6 per cent eosinophils, 2 per cent basophils, 26 per cent myelocytes, 1 per cent myeloblasts, 16 per cent large lymphocytes and 11 per cent small lymphocytes, and also tertian malarial parasites which were present at this examination.

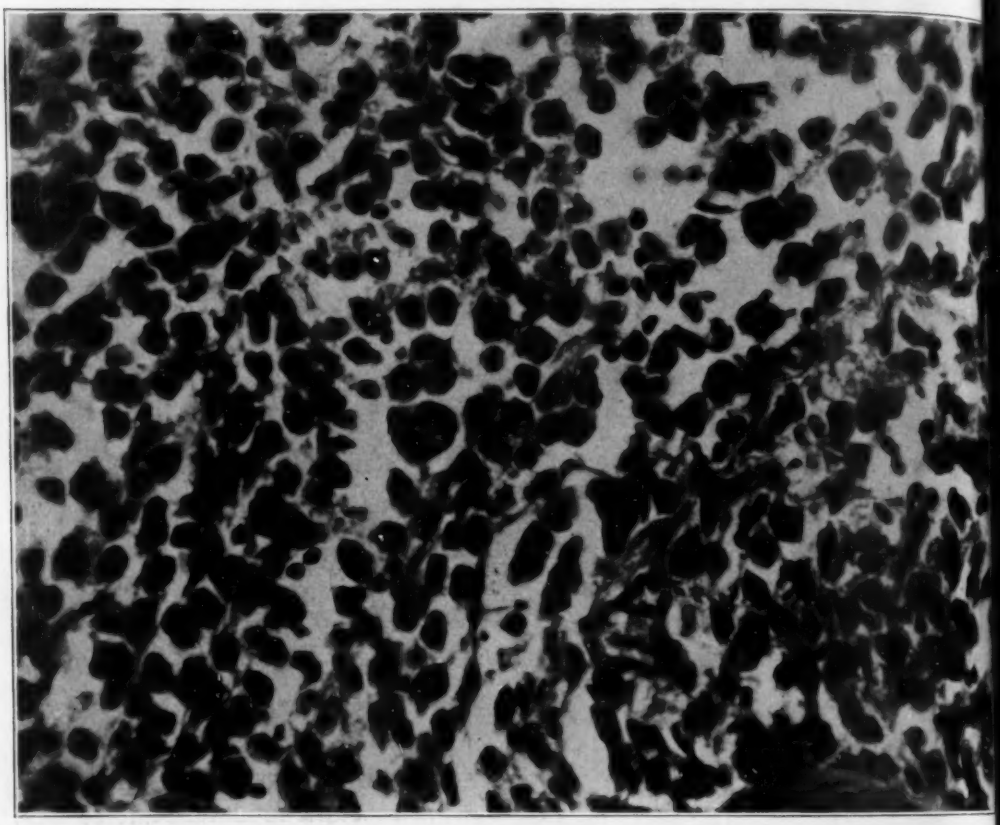

Fig. 35 (path. no. 44477).—Photomicrograph showing the original primary tumor of medullary carcinoma of the stomach which subsequently metastasized to bone.

A roentgenogram of the chest showed enlarged mediastinal glands, and at this time the long bones were normal. Chemical examination of the blood showed nothing unusual, and a Wassermann reaction was negative.

A lymph gland was removed for diagnosis, and the microscopic picture (fig. 34) was thought to be myeloid leukemia.

The further course of the disease was one of progressive emaciation. The anemia became very marked, and fifteen days after admission to the hospital the patient died.

Autopsy was performed, and a large tumor of the stomach with extension to surrounding tissue and mesentery was found. The retroperitoneal, mediastinal, peribronchial, cervical, axillary and inguinal lymph nodes, the spleen, liver and bone (table 9) were involved.

The microscopic picture of the tumor of the stomach (fig. 35) revealed a medullary type of carcinoma.

The bone marrow was diffusely destroyed, and it was easy to distinguish between bone marrow and tumor tissue.

Tumors of other parts of the gastro-intestinal tract occasionally metastasize to the skeletal system, which is represented in the literature by isolated case reports.[33]

TABLE 10.—*Malignant Disease of the Gastro-Intestinal Tract with Metastases to Bone*

Path. No.	Color	Sex	Age	Primary Tumor	Location of Metastases	Pathologic Fracture	Treatment of Metastases	Duration of Metastases
				Carcinoma of the Gastro-Intestinal Tract				
29861	..	..	..	Carcinoma of esophagus	Lumbar spine	.....	.....	.....
29861½	..	..	..	Carcinoma of cecum	Ischii and pubis	.....	.....	.....
29861¾	..	..	..	Carcinoma of sigmoid	Upper third of right femur	.....	.....	.....
5145	W	F	54	Carcinoma of rectum	Midshaft of right humerus	Humerus	.....	Living after 18 mo., lost from observation
				Sarcoma of Gastro-Intestinal Tract				
28258½	W	F	18 mo.	Sarcoma of ileum	Right ilium, left femur right femur, left ilium	.....	Radium	Dead
				Primary Carcinoma of the Liver				
25501	C	M	70	Carcinoma	Pelvis, upper end of femur, spine	.....	.....	Lived 6 mo.

Among the primary lesions in this laboratory, single examples of invasion of the bone from malignant conditions of the esophagus, cecum, sigmoid, rectum, ileum and liver are recorded (table 10).

The associated secondary deposits, as in the other primary tumors mentioned, were contributing factors in the ultimate prognosis of these cases. Only one patient in the series was treated by roentgen therapy, with some relief from pain but apparently without prolonging the patient's life.

33. Moon, V. H.: Primary Carcinoma of the Liver with Metastases to Bone, Arch. Path. **8**:938 (Dec.) 1919. Brickner, W. M., and Milch, H.: Pathological Fracture of the Humerus due to Carcinoma Metastatic from a "Silent" Growth in the Oesophagus, Internat. Clin. **1**:207 (March) 1926. Jenkinson (footnote 31).

CARCINOMA OF THE LUNG

Involvement of the bone was found in four (16 per cent) of twenty-four cases of carcinoma of the lung analyzed in this clinic. Grove and Kramer,[34] in a study of twenty-one cases of primary lesions of

TABLE 11.—*Miscellaneous Tumors with Metastases to Bone*

Path. No.	Color	Sex	Age	Primary Tumor	Location of Metastases	Pathologic Fracture	Treatment of Metastases	Duration of Metastases
					Carcinoma of the Lung			
40952	W	M	..	Carcinoma of lung	Lumbar spine, pelvis, skull	.....	X-rays	.....
37838	W	M	39	Carcinoma of lung	Right 9th rib	.....	Resection	Lived 21 mo.
31740	W	M	49	Carcinoma of lung	Ribs, vertebrae	2 ribs	.....	.....
14500	C	F	54	Carcinoma of lung	Skull	.....	Excision of frontal bone	.....
					Melanomas			
32176	W	M	44	Melanoma	Middle third of left humerus	Middle third of humerus	Amputation of left arm	Living 7 yr., 6 mo.
10764	W	F	79	Melanoma	Upper third of tibia	.....	.....	Lived 36 mo.
9717	W	M	70	Melanoma	Ribs, clavicle, radius	.....	.....	.....
					Nasopharyngeal Tumor			
40299	W	M	67	Adenoid cystic basal cell carcinoma	Skull, jaw, cervical vertebrae, clavicles, scapulae, all ribs, other bones	.....	Excision of nasal polyp, with radium	Lived approximately 36 mo.
					Epithelioma of Ear and Heel			
32025	W	F	40	Epithelioma	Lower end of femur	.....	Cauterization of lower end of femur, erysipelas and prodigiosus toxins (Coley's)	.....
30831	W	M	..	Epithelioma	Malar bone	.....	X-rays, radium	Lived 30 yr. plus
					Sarcoma of the Soft Part			
26686	W	M	32	Sarcoma of neck	Clavicle, lower right jaw, tibia	.....	X-rays, erysipelas and prodigiosus toxins (Coley's)	Lived 24 mo. plus
26683	W	M	33	Sarcoma of neck	Right clavicle, ilium, radius, left tibia, ankle	.....	X-rays	.....

the lung, found 38 per cent metastasizing to bone. A wide variety of bones were involved, including the lumbar spine, pelvis, ribs and skull (table 11). Pathologic fracture was found in the ribs of one case at examination.

34. Grove, J. S., and Kramer, S. E.: Primary Carcinoma of the Lung, Am. J. M. Sc. **171**:250 (Feb.) 1926.

The clinical course of the disease revealed nothing different from that recorded in other metastatic lesions. The x-ray picture shows destruction of the bone with slight formation of new bone, often within the area of destruction (fig. 36). Microscopically, the osseous lesion shows destruction of the bone by direct contact with the tumor cells and some attempt on the part of the bone to react by fibro-ostosis (fig. 37).

Fig. 36 (path. no. 14500).—Roentgenogram of the skull showing destruction of the bone with slight formation of new bone within the area of tumor invasion.

Hirsch and Ryerson [35] reported four cases in which the early diagnosis was that of "endotheliomas" of bone, and they urged complete autopsies in all so-called primary endothelioma of the bone in order to rule out metastases from tumors of the lung.

In one case, pain was relieved by excision of the affected bone.

35. Hirsch, E. F., and Ryerson, E. W.: Metastases of the Bone in Primary Carcinoma of the Lung: Review of So-Called Endotheliomas of Bone, Arch. Surg. **16**:1 (Jan., part 1) 1928.

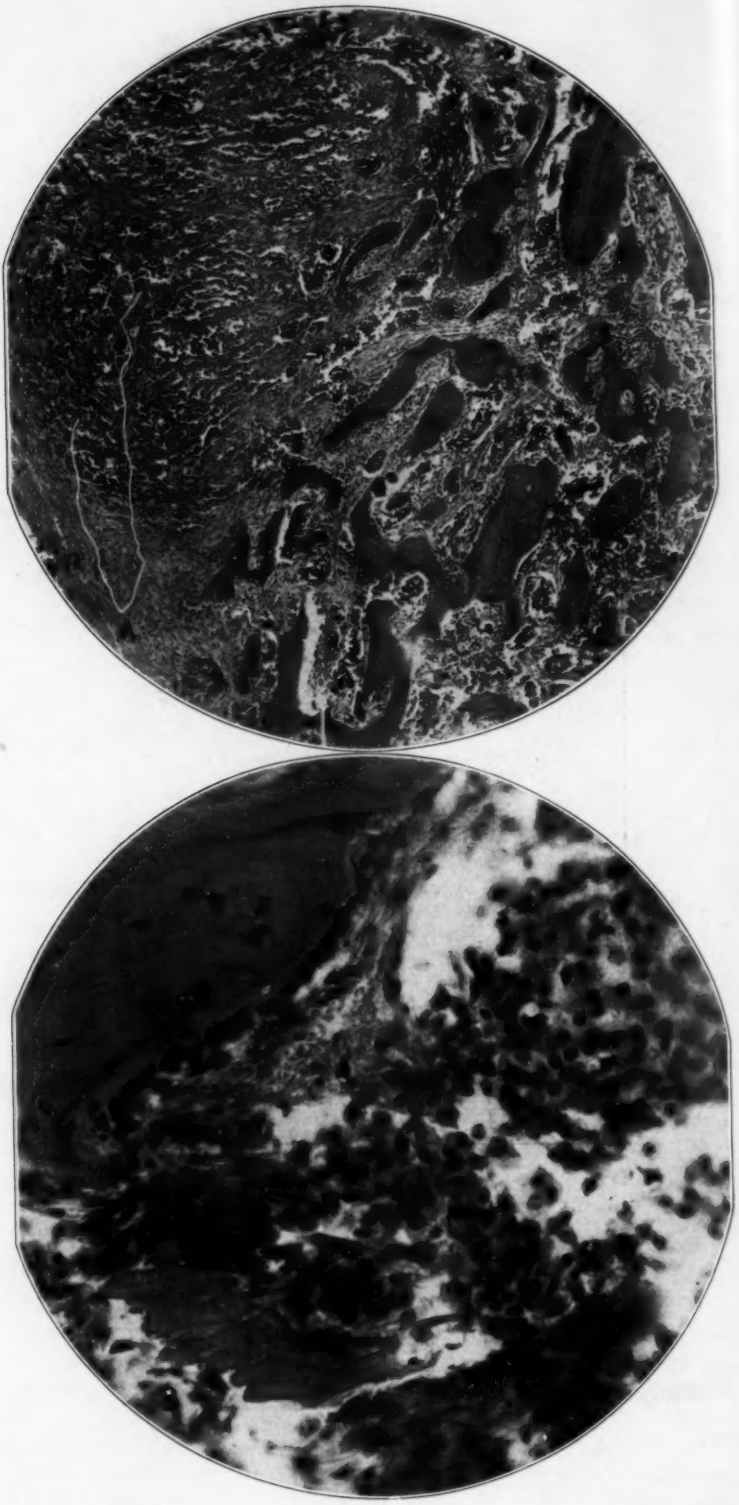

Fig. 37 (path. no. 14500).—*A*, photomicrograph showing the destruction by direct contact with the tumor cells while in areas some attempt is seen on the part of the bone to react by fibro-ostosis. *B*, high magnification of a bone spicule being destroyed by tumor. Note the direct contact between the tumor cells and the osteoid structure.

OTHER PRIMARY TUMORS

Melanomas.—Melanoma developing in a benign pigmented mole is not unusual, but few examples are cited in which metastasis to bone occurs. In 169 cases in this laboratory, only 3, or 1.07 per cent, showed secondary deposits in bone (table 11).

The location in the long bones is about the site of the nutrient vessels (figs. 38 and 39), with marked destruction and expansion of the bone and some invasion of the soft part.

Fig. 38 (path. no. 32176).—Roentgenogram of a melanoma involving the midshaft region of a humerus. One may observe the marked destruction of the bone with pathologic fracture in this region. At the attachment of the deltoid muscle is seen convex bowing of the bone with subperiosteal formation of new bone on the lateral aspect.

Pathologic fracture occurred in one instance in the middle third of the humerus (fig. 38).

The clinical features of this type of metastasis is one of pain extending over a period of a year or more, occasionally pathologic fracture and ultimately the symptoms of generalized dissemination of cancer. However, there is a patient living seven years and six months following

amputation of the left arm (fig. 38) for a metastatic lesion in the middle third of the humerus (path. no. 32176).

A white man, aged 44, had pain in the middle of the left humerus eight weeks prior to admission. Swelling began soon after and was accentuated by the use of the arm. The examination gave negative results, except for the left arm, where there was a cylindric swelling in the middle third with slight local redness of the skin. The pathologic fracture was found at this examination.

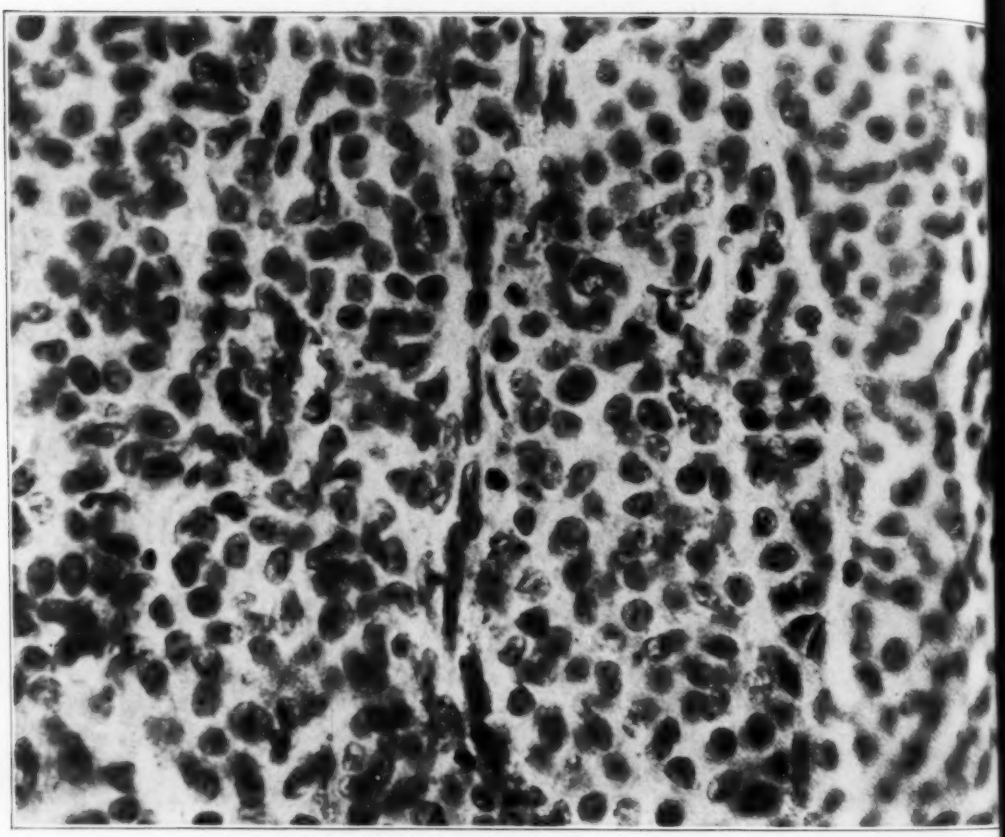

Fig. 39 (path. no. 32176).—Microscopic picture of the tumor depicted in figure 38, showing cells with the morphology of melanoma. Melanin pigment can be seen incorporated in many of the cells.

The arm was amputated, and the microscopic examination (fig. 39) revealed cells with the morphology of melanoma.

Melanotic pigment was found[36] incorporated in many of the cells. No

36. Smith, D. T.: Method for Making a Differential Diagnosis Between Xanthomatous and Melanin Tumors from Frozen Sections, Arch. Surg. **8**:908 (May) 1924.

Fig. 40 (path. no. 40299).—*A* and *B* show an invasion of the skull, pelvis and upper ends of the femurs from an adenoid-cystic, basal cell carcinoma of the nasopharynx. Note the combined destruction and formation of bone within the areas of metastases.

further treatment was instituted, and in January, 1930, the patient was reported well, seven years and six months after the onset of symptoms.

Other isolated examples of metastases from various primary tumors to bone are recorded in the laboratory and are shown in table 11.

An interesting nasopharyngeal tumor of the adenoid-cystic basal cell carcinoma type is to be noted, which after several recurrences and much radium therapy with excision of the primary nasal polyp on many occasions has ultimately metastasized to the skeleton, the patient having lived thirty-six months from the onset of the osseous invasion. The bones involved were the skull, jaw, cervical vertebrae, clavicles, scapulae, all of the ribs, pelvis and femurs (fig. 40).

Dr. John W. Spies of the surgical pathology department of Yale University, in a personal communication, stated that he had collected a large number of these cases. He found that the tumors are usually situated in the region of the nasopharynx or about the buttocks, and that many of them metastasize after repeated recurrences.

METASTASES FROM AN UNDETERMINED MALIGNANT CONDITION

In many instances the clinician is unable to diagnose definitely the lesion of the bone after a thorough examination has been made and roentgenograms of the entire skeleton examined. Even when a biopsy is taken, the morphologic structure of the cells in the microscopic picture are such that little more can be said than that a metastatic lesion is present.

There are thirty-one such cases under analysis in this laboratory, and in none of them is it possible to determine the primary focus. The roentgen criteria in the differential diagnosis of lesions of the bone, as pointed out previously in this paper (see section on breast), plus clinical and laboratory studies, have usually aided in classifying these lesions as metastatic to bone, though in all instances the true nature of the disease is left subjudice (tables 12 and 13).

Little can be gained from detailed analysis of this group. It is to be pointed out, however, that many of these patients were relieved from symptoms of pain for long periods by the administration of roentgen therapy, and in a few instances (path. nos. 39856, 35310, 27929 and 30857), the patients lived from three to eight and a half years following roentgen therapy or amputation of the affected part.

MODE OF METASTASES

Since the time of Virchow and his fundamental work on the knowledge of tumors, many attempts have been made to explain secondary

TABLE 12.—*Cases of Undetermined Primary Lesions with Metastases to Bone*

Path. No.	Color	Sex	Age	Primary Tumor	Location of Metastases	Pathologic Fracture	Treatment of Metastases	Duration of Metastases
43226	W	M	45	Carcinoma	Upper third of left femur, left ilium	Left femur	Exploration	.....
42924	..	M	58	Undetermined	1st lumbar vertebra	.....	Laminectomy	.....
42706	W	M	56	Undetermined	Left femur	Left femur below trochanter	.....	Lived 10 mo.
40816	W	F	48	Undetermined	All ribs, dorsal spine, lumbar spine, cervical spine, ilium, scapula, clavicles, humeri, femora	.....	X-rays and lead	.....
40734	..	F	..	Undetermined	Skull, pelvis, thoracic vertebrae, femur, ribs	Ribs, femur	.....	Lived 15 mo.
39914	W	M	60	Undetermined	Right humerus, left humerus spine	Right humerus	X-rays	.....
39856	W	M	21	Undetermined	Skull, upper third of right femur	Upper third of right femur	X-rays	Lived 80 mo.
39506	W	F	66	Undetermined	Ilium, left acetabulum	Ilium	X-rays	Lived 27 mo.
39038	..	M	24	Sarcoma	Right temporal bone	.....	.....	.....
38468	W	M	42	Undetermined	Shaft, humerus and right femur	.....	.....	Lived 48 mo.
37880	W	F	70	Undetermined	Upper third of left femur	Femur	.....	.....
36178	C	F	58	Carcinoma	Middle third of right femur	Femur	Amputation of right leg	Lived 15 mo.
36118	W	M	49	Carcinoma	Shaft of femur	Femur	Curettement	Lived 24 mo.
35838	..	..	..	Undetermined	9th dorsal vertebra, rib, femur	.....	.....	.....
35618	W	F	..	Undetermined	Upper third of left femur, tibia, fibula, left pubic bone	Femur	X-rays	Lived 21 mo.
35310	W	M	..	Undetermined	Humerus	.....	Prophylactic toxin treatment, biopsy and amputation	Living 45 mo.; 1928
35002	W	M	28	Undetermined	Pelvis, 4th lumbar vertebra	.....	.....	.....
34992	W	F	35	Carcinoma	Right clavicle	.....	X-rays	Lived 8 mo.
34300	W	M	67	Colloid carcinoma	Upper third of right humerus	.....	Amputation of right arm	.....
34101	W	M	..	Carcinoma	Clavicle	.....	Resection of tumor	.....
32792	W	F	45	Carcinoma	Frontal bone, scapulae, ischia, fibulae	.....	.....	.....
32446	W	F	..	Carcinoma	Ilium	.....	.....	.....
32229	W	F	40	Undetermined	4th cervical vertebra, 6th dorsal vertebra, ribs, 9th and 12th left, 7th right, femora, left clavicle, ilium	.....	.....	Lived 24 mo.
31018	W	M	55	Undetermined	Left clavicle	Clavicle	Radium, x-rays	.....
30943	..	M	..	Undetermined	Upper third of femur, ilium, and sacroiliac joint	.....	X-rays	.....
30867	W	F	32	Carcinoma	6th thoracic vertebra	.....	Laminectomy	.....
30857	W	M	52	Undetermined	Ilium, spine	Ilium	X-rays	Lived 36 mo.
30654	W	M	70	Carcinoma	Right clavicle	Clavicle	.....	.....

TABLE 12.—*Cases of Undetermined Primary Lesions with Metastases to Bone—Continued*

Path. No.	Color	Sex	Age	Primary Tumor	Location of Metastases	Pathologic Fracture	Treatment of Metastases	Duration of Metastases
29831	W	F	56	Carcinoma	4th, 5th and 6th cervical vertebrae, skull	.....	X-rays, exploration of skull	Lived 8 yr. 4 mo.
28864	W	M	42	Sarcoma	Midshaft of right femur	Femur	Neoarsphenamine, plaster cast	Lived 4 mo.
27929	W	M	29	Carcinoma	Upper third of right tibia, 6th and 7th dorsal vertebrae	.....	Amputation of right leg	Lived 98 mo.; 10 mo. after amputation
27576	..	M	46	Carcinoma	Rib	.....	Excision of tumor	.....
26264	W	F	54	Carcinoma	Right ilium, right clavicle, cervical vertebra, left parietal bone	.....	Baking, massage, x-rays	Lived 10 mo.
20225	W	M	55	Undetermined	Upper third of right humerus	.....	Antisyphilitic therapy	.....
16245	W	F	49	Carcinoma	Right clavicle, left rib, right tibia, phalanx, right great toe, ilium, sacrum, femur, right rib	.....	Electrical therapy, nonspecific protein therapy	Lived 20 mo.
6830	W	M	50	Carcinoma	Humerus, metatarsal bone	Humerus	Curettement metatarsal bone	.....
1382	W	M	43	Carcinoma	Scapula	.....	Amputation of arm with clavicle and scapula	Lived 7 mo. 2 wk.

TABLE 13.—*Involvement of Bone in Thirty-Seven Cases of an Undetermined Primary Malignant Disease*

Bone Involved	Number of Cases	Number of Times	Right	Left	Undetermined Side
Pelvis					
Location (?)	2	2	..	..	2
Ilium	9	9	1	2	6
Ischium	1	2	1	1	..
Pubis	1	1	..	1	..
Sacro-iliac joint	1	1	..	..	1
Acetabulum	1	1	..	1	..
Sacrum	1	1	..	..	1
Femur					
Location (?)	7	8	3	2	3
Upper third	5	5	1	3	1
Middle	3	3	2	..	1
Spine					
Location (?)	2	2	..	..	1
Cervical	4	4 (twice; number not stated)			..
Thoracic	5	5 (twice; number not stated)			..
Lumbar	3	2 (once; number not stated)			..
Clavicle	8	8	5	3	1
Humerus					
Location (?)	5	6	2	2	2
Upper	2	2	2	..	..
Middle	1	1	..	..	1
Lower	..	..	..	..	..
Rib	7	..	..	..	..
Skull	6	5	1	1	3
Tibia					
Location (?)	2	2	1	1	1
Upper	2	1	1	..	..
Scapula	3	4	1	1	2
Fibula, location (?)	2	3	1	1	1
Phalanx	1	1	1	..	1
Metatarsal	1	1	1	..	1

metastatic lesions. Von Recklinghausen [37] was among the first to champion the theory of the spread of malignant tumors by the blood stream into the bone marrow, and his deduction was based on the three following points: 1. Metastases in bones occur within the medullary cavity and reach the periosteum only by extension from the interior. 2. When the subperiosteal tissue is invaded, it is always in the region of the large foramina, which serve as a point of egress for the veins. 3. The individual cancer cells in the marrow lie within definite channels, which are arranged in a manner similar to that of the veins present in the marrow.

Proof that the tumor cells lay within the small venous channels was based on the fact that von Recklinghausen could find no blood channels free from the tumor in the invaded areas, and that no known lymphatic channels had been found to exist within the medullary cavity.

Since 1891, there have been many advocates of this theory of the mode of metastases, Paget,[38] Piney [7] and Schmidt [39] being prominent among the pathologists who favored this view. Piney,[7] in 1922, set forth further evidence in favor of metastases by the blood stream. An anatomic and histogenic analysis was made of the bone marrow, and he found that at birth all of the bones of the skeleton except those of the cranium contained red marrow in which there was no microscopic fatty tissue, and as the person's age increased deposits of fat appeared in the marrow but were not present in equal amounts in all of the bones. In the adult, the vertebrae, sternum, pelvis and most of each rib contained red cellular marrow, the only red marrow in the long bones of the limbs being found in a small area at the upper end of the diaphyses. The small bones of the hands and feet showed complete conversion into fat at a much earlier date. In the bone marrow, he was able to find vascular channels but no evidence of lymphatic vessels. Within the vascular channels, plugs of epithelial cells were found both in the bone marrow and at the sites where the veins emerged through the foramina—points at which carcinomatous metastases reached the surface. These changes were cited by him as evidence in favor of the embolic theory. He set forth the observation of the lack of bone marrow in the small bones of the extremities as a major reason for the paucity of metastases in those regions.

Sampson Handley,[10] in a treatise on cancer of the breast, in 1906, for the first time presented the view that cancer is disseminated by

37. Von Recklinghausen, F.: Die Fibrose oder deformierende Ostitis die Osteomalacie und die osteoplastiche Carcinöse in ihren gegenseitigen Beziehungen, Festschr. der Assistenten für Virchow, 1891, p. 17.

38. Paget, S.: The Distribution of the Secondary Growths in Cancer of the Breast, Lancet **1**:571 (March) 1889.

39. Schmidt, M. B.: Die Verbreitungswege der Karzinome, Jena, Gustav Fischer, 1903.

permeation of the lymphatics, and was of the opinion that the majority of metastases to the bone occurred by direct extension of the tumor cells through the deep fascial lymphatics; that both the humerus and the femur were invaded at points usually in the region where the bone lies nearest the deep fascia or at the point where it comes nearest to the cutaneous surface, and that the bones beneath the knee and elbow were rarely involved, owing to a fatal termination of the case before the invasion of the lymphatics reached these distant locations.

Following this contribution, there have been many advocates of this explanation. Among the more recent investigators, Carnett and Howell [13] have supported the theory of lymphatic permeation, with one exception: in the case of neoplastic extension within the abdomen they have found the cancer cells permeating the retroperitoneal lymphatics, and in no case have they found the extension of tumor by transcoelomic transplantations as was suggested by Handley. This study is of particular interest in that complete roentgenographic studies were made of a large series of cases of mammary cancer showing metastases in the bone, and they have emphasized the fact that invasion seems to occur first in the region of the primary tumor, with subsequent involvement of other bones in juxtaposition to those already invaded. However, it must be noted that the majority of their cases were in the late stages of the disease, so that either operation was impossible or radical operation was deemed futile.

In the literature cases are recorded with the idea of establishing either the embolic or the lymphatic mode of metastases, and in some instances pathologists, notably Ewing,[40] have stated that both modes of transmission obtain.

In the analysis of carcinoma of the breast with metastases to the skeletal system in this laboratory, certain facts are presented with a view to verifying the mode of metastases consistent with the data at hand.

Clinically, it was found that the majority of the patients had been treated by radical amputation of the breast early in the disease, and thus many of the lymphatics which might have been a source of tumor invasion were destroyed. This observation is borne out when one comes to study the incidence of bony involvement and finds relatively few of the osseous metastases are in the immediate region of the primary tumor.

When the pelvic bones were involved, there was not infrequently an associated invasion of the heads of the femurs (fig. 15), and the gross and microscopic study in some of these instances showed direct involvement by means of the ligamentum teres, thus establishing further proof that there is an extension of tumor from one bone to another via the lymphatics as well as extension from the primary tumor to the

40. Ewing (footnote 26, pp. 77-96).

regional bones as pointed out by Carnett and Howell. But when one studies the long bones, such as the humerus and the femur, and less frequently the bones of the forearm and those below the knee, especially in the case of single lesions, and notes the absence of invasion in the intervening structures between the primary focus and the distant metastases, one is forced to the conclusion that a vascular route furnished the mode of metastases.

Other groups of primary lesions metastasizing to bone as found in this study have substantiated the facts brought out in the analysis of lesions of the breast and in addition have emphasized in the roentgen and gross study the relation of the nutrient vessels to the metastatic lesions, as well as establishing proof that many bones are invaded by direct extension of the tumor through the lymphatics.

TABLE 14.—*Metastases to the Bone*

Primary Malignant Conditions	Number of Cases	Osseous Metastases: Number of Cases	Osseous Metastases: Per Cent of Cases	Pathologic Fracture: Number of Cases	Pathologic Fracture: Per Cent of Cases	Patients Living Over Five Years: Number	Patients Living Over Five Years: Per Cent
Mammary carcinoma	1,914	100	5.2	15	15.0	1	1.0
Prostatic carcinoma	1,040	134	12.8	3	0.2	0	0
Carcinoma of the stomach	537	7	1.3	1	14.3	0	0
Colon and rectal carcinoma	497	3	0.006	1	33.3	0	0
Melanoma	169	3	1.77	1	33.3	1	33.3
Uterine carcinoma	86	5	5.6	0	0	0	0
Hypernephroma	63	22	34.9	10	45.4	1	4.5
Ovarian carcinoma	60	1	1.6	0	0	0	0
Testicular sarcoma	42	1	2.4	0	0	0	0
Carcinoma of the lung	24	4	16.6	1	25.0	0	0
Ovarian sarcoma	15	1	6.6	0	0	0	0
Malignant disease of thyroid	15	6	4.0	2	33.3	0	0
Testicular carcinoma	13	1	7.7	0	0	0	0
Undetermined malignant disease	..	37	...	15	40.5	2	5.4
Nasopharyngeal carcinoma	..	1	...	0	0	0	0
Squamous cell carcinoma	..	2	...	0	0	1	50.0
Sarcoma of the soft part	..	2	...	0	0	0	0
Carcinoma of the bladder	..	1	...	0	0	0	0
Esophageal carcinoma	..	1	...	0	0	0	0
Ileac sarcoma	..	1	...	0	0	0	0
Carcinoma of the liver	..	1	...	0	0	0	0

With these facts set forth, it would seem that one must accept both an embolic and a lymphatic mode of involvement, and that the particular circumstances of each individual case, such as the duration and the character of primary tumor, together with the method of treatment, will often determine the mode of metastases.

SUMMARY

Three hundred and thirty-four metastatic lesions of bone have been studied with a view to setting forth the important clinical features, x-ray picture, incidence of involvement of the bone, histogenesis, mode of metastases and results of treatment.

One hundred carcinomas of the breast with secondary involvement of the bone were studied. The majority of the primary lesions were

found microscopically to be of the scirrhus type (fifty-eight), with a few instances of adenocarcinoma (six cases), medullary carcinoma (four cases), comedocarcinoma (three cases) and colloid carcinoma (two cases). In one patient, the primary lesion was found to be fibrosarcoma.

The bones most often involved were, in the order of frequency: the spine, pelvis, femur, skull, ribs and humerus, while metastases in the forearm and the lower leg were of infrequent occurrence.

Clinically, pain of a severe rheumatic character was an important feature. When the metastatic foci were located about the spine, girdle pains and many other neurologic manifestations appeared. Occasionally, pain preceded roentgenologic evidence of skeletal metastases from three to eighteen months. The majority of the cases eventually showed a secondary type of anemia with its complications as the disease progressed. In an occasional case reported in the literature it was pointed out that a pseudopernicious type of anemia was present. The terminal phases of the disease were a progressive emaciation, usually with much pain; when the lungs were involved (nineteen cases), respiratory embarrassment with spitting of blood and paroxysms of coughing were added features of discomfort.

Pathologic fracture occurred in fifteen instances, thirteen being in the femur, one in the ilium and multiple fractures of the ribs in the other case.

As shown by the roentgenogram, metastatic lesions of the bone from carcinoma of the breast were found most often to be multiple, presenting themselves as a single focus in only one fourth of the cases. The majority of the solitary foci were in the vertebrae or femur. Two types of metastatic lesions were discussed (osteolytic and osteoplastic). The osteolytic form of metastatic deposit appeared to be the more common one, and in the long bone both types were often found well above the average entrance of the nutrient artery in the case of the femur and above or below it in the case of the humerus. Mottling representing an increase in the density of the bone was often found within the areas of destruction, together with thickening of the cortex above or below the site of metastasis, and it was pointed out that microscopically this proved to be an attempt at osseous repair or fibro-ostosis. The pelvis, vertebrae, skull, ribs, scapulae, clavicles and sternum showed the same typical medullary involvement as those of the femur and humerus. Lack of distortion or bending of the bones was evidenced, due partly to the advanced stage of the disease, partly to roentgen therapy so frequently resorted to and partly also to the age of the patient; fracture was therefore the rule.

The gross and microscopic pathologic changes in the affected bones studied in this laboratory have been described in detail, and abundant evidence was found in favor of a natural tendency of bone to react by fibro-ostosis in an effort to protect itself from further invasion and to rebuild the part already destroyed (fig. 18). It has also been pointed out that following the application of roentgen therapy many of the affected bones revealed a sclerosing or healing reaction.

The differential diagnosis of lesions of the bone from a roentgenographic point of view has been discussed.

Treatment has been emphasized, the patients being divided into three groups: (1) those who first had a radical amputation of the breast; (2) those who had only simple amputation or local excision; and (3) those on whom no operation was performed and who received only various forms of palliative treatment. The therapy as outlined was based on the clinical experience of Dr. J. C. Bloodgood and Dr. Max Kahn. The results obtained from roentgen therapy were relief from pain in many instances and a definite prolongation of life. Resection of the affected part apparently had no effect on the duration of life, but gave relief from excruciating pain.

Sixty-three cases of hypernephroma have been reviewed, and in twenty-two instances skeletal metastases were found. The bones usually affected, in the order of their frequency, were: humerus, spine, femur, pelvis, ribs, bones of the feet, skull and sternum.

The clinical course has been illustrated by a typical case report.

Pathologic fracture occurred in ten patients (45.4 per cent); six times in the femur, three times in the humerus and in one instance multiple fractures of the ribs. In one case, spontaneous pathologic fracture was the first symptom referable to the disease.

The lesions of the bone appeared in the roentgenogram either as single or multiple foci, located in one or more bones. Secondary deposits were found as a single focus in a long bone in the majority of cases (59 per cent). It was pointed out that many of these lesions were at the site of the nutrient vessels, as well as in the heads of the femur and humerus, together with associated metastases of the pelvis in many cases. Little evidence was found in metastases of the bone from hypernephroma of any attempt at fibro-ostosis or formation of new bone within the area of destruction. Early involvement was always represented by a distinct medullary defect, periosteal changes in the roentgenogram being exceptionally rare.

Evidence has been presented to substantiate a hematogenous route of metastatic invasion. Irradiation alone offered as great a chance for the prolongation of life in this group of cases as did surgical intervention alone or surgical measures combined with roentgen or radium therapy.

Metastases of bone as seen in the various cases of primary malignant disease in the male and female genital tract have been presented in detail.

Osseous lesions in carcinoma of the prostate were found most frequently in the pelvic bones, vertebrae and femurs. The patients showed obstructive urinary symptoms and enlargement of the prostate at the time the metastases were noted, with a subsequent progressive emaciation, secondary anemia and excruciating pain in the affected bones. As depicted in the roentgenogram, the metastatic lesions in the bones were predominantly osteoplastic, a characteristic phenomenon in bony deposits from prostatic cancer. On gross examination, these metastatic areas were usually white or grayish nodules, surrounded and interspersed by a marked healing of the bone. This reaction was found to be quite the reverse of that usually seen in other metastatic lesions, and the possibility that the invasive powers of the metastatic tumor were of such moderate character that the bone was allowed to proliferate with sufficent rapidity to keep apace with the invasion of the tumor was set forth as an explanation of this phenomenon. Roentgen therapy offered relief from pain, but was not effective in eradicating the lesion or in greatly prolonging the life of the patient. Resection and amputation offered only comfort.

Malignant disease of the testicle with metastases to bone was found to be rare, occurring once in carcinoma of the testicle, and the same incidence was found in sarcoma of the testicle. Case reports were given to illustrate the clinical course. The x-ray picture revealed a destructive type of lesion. In the one case of carcinoma of the testicle with metastases to bone, roentgen therapy seemed to have prolonged life and to have aided the bone in reacting to the tumor growth by recalcification, while the patient with sarcoma of the testicle with osseous deposits received no definite benefit from irradiation and died in a short time following this treatment.

One example of carcinoma of the bladder with metastases to bone has been cited, and its clinical course pointed out.

Five of eighty-six cases of carcinoma of the uterus showed metastases to bone. Two primary tumors were located in the cervix. Clinically varying degrees of pain with disturbance of use in the affected extremities were common symptoms. The clinical course of the advancing disease was dominated by secondary invasion of surrounding organs. The x-ray picture was one of destruction of bone. Treatment proved particularly unsatisfactory in this group of cases.

Two instances of ovarian malignant disease with metastases to bone were found among sixty-nine such cases in this laboratory. Case his-

tories have been presented to illustrate the various clinical features and ultimate clinical course. Roentgen therapy proved of some benefit in one instance.

Involvement of the bone secondary to a malignant condition of the thyroid was found to be of rather frequent occurrence, as presented in the literature.

The clinical course was usually one of progressive emaciation with symptoms referable to the bones that were the seat of metastases. Respiratory symptoms were often prominent when the gland had invaded structures of the neck and mediastinum. The usual microscopic picture of an osteolytic type of metastatic lesion was pointed out. Roentgen therapy proved to be of little avail.

Only 7 in a series of 537 patients who were found to have carcinoma of the stomach presented metastases to the bone. The frequency of involvement of the ribs without metastases to the lungs has been pointed out as an illustration of the lymphatic mode of dissemination. In one instance, a pathologic fracture was found at the lower third of the right femur. A case report has been presented to illustrate the clinical course. An interesting feature of the blood in carcinoma of the stomach with metastases to bone has been pointed out, and a case which showed this type of blood picture has been reported.

Other parts of the gastro-intestinal tract showed an occasional predilection for the skeletal system, which included single examples of malignant conditions of the esophagus, cecum, sigmoid, rectum, ileum and liver.

Carcinoma of the lung with metastases to bone was found in only four patients in a study of twenty-four cases. A wide variety of bones were involved, including the lumbar spine, pelvis, ribs and skull. Pathologic fracture was found in the ribs in one case on examination. The clinical course of the disease revealed nothing unusual and was similar to that reported in other metastatic lesions. The x-ray picture showed destruction of the bone with slight formation of new bone, often within the area of destruction. In one case, relief from pain was obtained by excision of the affected bone. Other treatment in this group of cases was not recorded.

Other primary tumors with metastases to bones were melanoma, adenoid cystic basal cell carcinoma of the nasopharynx, epithelioma of the ear and heel and sarcoma of the soft part in the region of the neck.

A group of cases with metastases to bone from some undetermined malignant condition have been presented, and it was pointed out that little could be gained from a detailed analysis of this group, but that in many of these cases roentgen therapy gave relief from pain for long periods.

The modes of metastases have been discussed in detail. The analysis of the cases of carcinoma of the breast with metastases to the skeletal system together with other groups of primary lesions metastasizing to bone was set forth in order to emphasize certain facts with the purpose of verifying the mode of metastases which was consistent with the data at hand. It has been pointed out that both an embolic and a lymphatic mode of involvement were responsible for metastatic lesions of the bone, and that the particular circumstances of each case often determined the mode of invasion.

RETROPERITONEAL TUMORS

REPORT OF CASES *

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All cases that present puzzling diagnostic problems are of interest, but this is especially true of cases in which there is known to be an abdominal tumor or in which a tumor is found at operation or autopsy. To the surgeon, the abdominal tumor is of particular interest. He wants to know if it is removable; if so, whether removal will result in permanent cure, and whether by the time the diagnosis is made if secondary growths have formed in other localities which will make cure impossible. It is of interest to know whether the tumors are primary or secondary to a growth at a distance. It is also of interest to know whether they represent local manifestations of general disease.

Because of personal experience, which will form the subject of this paper, I venture to discuss, under one title, some observations that may seem unrelated except for the fact that an abdominal tumor has been present at some stage of the disease.

The group to be discussed will include: (1) retroperitoneal lymphoblastoma (Hodgkin's type) (L. E. L.); (2) lymphosarcoma, apparently originating in the retroperitoneal glands (Miss A.); (3) metastatic tumors of the retroperitoneal lymph glands following teratoma of the testicle (Mr. R.); (4) retroperitoneal sarcoma, secondary to sarcoma of the thigh (Mr. J. L.), and (5) retroperitoneal sarcoma (J. P.).

The first case to be presented should be an incentive to attempt to interpret symptoms better. A review of this case will certainly serve as a shock to any one satisfied with his diagnostic ability, if there is such a person.

The diagnosis was not suspected by any one of the many who saw the patient, and I confess that were I to see another such case I could not now do more than make a guess at the correct diagnosis. I have reviewed the history many times in its entirety and in summary in an effort to find something that might lead to an understanding of the sequence of events so that others might profit by my lack of diagnostic acumen. The end-result is that I am unable to offer many suggestions

* Submitted for publication, Jan. 8, 1931.
* Presented at the meeting of the Southern Surgical Association, Lexington, Ky., Dec. 11, 1930.

that might clear up the problem, hence I am presenting it for consideration by others.

This case like the others that are reported again proves that the abdomen is a mystery box. The autopsy first revealed the retroperitoneal mass which proved to be a lymphoblastoma. One might well label this case a diagnostic puzzle since so many problems were presented for consideration. When each problem seemed about to be solved, another mystery would appear. The physical signs were at no time in accord with the symptoms. The patient's personal experiences and convictions were factors that affected his emotions to such an extent that it was difficult to evaluate the effects of the disease.

RETROPERITONEAL LYMPHOBLASTOMA (HODGKIN'S TYPE)

CASE 1.—I had an opportunity to observe this patient for six years. My first contact was in 1924, at which time he was complaining of digestive disturbances, severe abdominal pain, particularly in the right iliac region, sour eructations, nausea, vomiting and violent abdominal cramps of short duration. He had had similar attacks for twenty years. Ten years before, such an attack persisted for a week.

A roentgen examination at this time showed a marked pylorospasm and a forty-eight hour stasis in the colon.

An appendectomy was done. A short meso-appendix and an appendix that was curled on itself were found. There was an anomolous peritoneal fold which formed a tunnel in which the appendix was hidden from view.

The postoperative convalescence was stormy, particularly because it was necessary to catheterize the patient for several days. Even after his bladder was emptied he had pain which seemed to be out of all proportion to any physical sign. He was fearful of pain.

In November, 1925, he complained of nausea, vomiting and pain which seemed to be relieved by food.

Again in 1926, he complained of nausea before meals. Food would satisfy his discomfort. He also complained of headaches and dizziness. I could find neither physical signs nor roentgen evidence to verify the clinical symptoms which seemed to point to a duodenal ulcer. Efforts were made to treat what I believed to be evidence of an egocentric syndrome. The patient's condition improved under rest, diversion and sedatives.

In December, 1928, he complained of a gnawing pain in the right side of his abdomen two or three hours after eating. He would have pain at night which was sufficient to awaken him, fulness after eating and distention. At times the pain was relieved by eating.

A visualization test of the gallbladder was done, and a report suggesting gallbladder disease was received. There was no evidence of a filling defect anywhere in the gastro-intestinal tract.

On the belief that the emotions might have something to do with his syndrome, the patient was referred to Dr. Lemann for consultation. Dr. Lemann was impressed with the predominance of emotional disturbances and treated him accordingly.

In spite of medical treatment, the symptoms persisted, in fact they became progressively worse. As a last resort it was thought necessary to investigate surgically, and a diseased gallbladder was found. Cholecystectomy was done in

March, 1929; the immediate postoperative course was uneventful. During the patient's convalescence at home, the disease ran a febrile course which was remittent in character. The remissions varied between 99 and 103 F. Urination was frequent and painful. Pus was found in the urine. Marked loss of weight followed an almost complete anorexia.

As it was thought that cystitis and pyelitis were responsible for some of his symptoms, the patient was brought back to Touro Infirmary where Drs. Hume, Pratt and Burns examined the genito-urinary tract. Ureteral obstruction was not found, and cultures from the ureters were repeatedly negative in spite of the fact that pus was found in the urine from the bladder. The urologists suggested that there must be some other source of sepsis than the kidneys.

The leukocyte count varied between 10,250 and 8,500; the neutrophils, between 75 and 85 per cent. Anemia was progressive. Vomiting was persistent. The only way fluid could be supplied was by hyperdermoclysis and intravenous infusions. Chemical examination of the blood presented neither evidence of an acidosis nor alkalosis. At all times the abdomen remained soft.

Fluoroscopic examination showed that the diaphragm was not elevated and both sides seemed to rise and fall normally with respiration. The liver was not palpably enlarged.

From the foregoing evidence we could not believe that a subphrenic abscess, perinephric abscess or an abscess of the liver existed. It did not seem plausible that any other intraperitoneal condition existed such as a subhepatic abscess secondary to the operation or that even an accumulation of the infected bile could be responsible for such a condition. This conclusion seemed to be justified because I believed that some rigidity and probably a palpable mass in the hypochondrium would have been found if either of the latter conditions had existed. There was no jaundice, and the stools were not lacking in color.

Blood cultures were negative. There was a normal or slightly elevated leukocyte count. Septicemia did not seem, therefore, to be a likely diagnosis. The chest remained free from physical signs that would have been present if an empyema or pulmonary condition had been responsible factors. Fluoroscopic examination of the chest by Dr. Henderson showed the pulmonary field to be clear.

On May 2, after all possible causes which could be suggested had been eliminated, including one which was persistently referred to by one of the consultants (multiple abscesses of the kidneys), it was decided, after consultation with Dr. C. Jeff Miller, to do an exploratory operation as a last resort to investigate the conditions about the liver and in the vicinity of the original operative site. Dr. Miller, at the consultation, had suggested that there might possibly be a slight puddling in the vicinity of the cystic duct or near the head of the pancreas.

The incision was made in the upper portion of the previous operative wound. There were no adhesions between the peritoneum and the liver, and a cavity was immediately reached, the lower boundary of which was the stomach, and the upper boundary the liver. The suspensory ligament was free from adhesions.

The liver was large, smooth and red, and evidence of abscesses on the surface was not found. The hand could easily be introduced between the liver and the diaphragm in either direction. Adhesions were not seen between the dome of the diaphragm and the liver. There was only one place in the upper portion of the liver that felt more prominent than the remaining portion, and this was near the midline.

The examining hand was then introduced into the cavity; no fluid accumulation of any kind was found. The stomach was retracted, and we were able to see in the depths that there was nothing suggestive of an abscess. Examination was made by Dr. Miller, who found nothing abnormal. Both of us noted some

Fig. 1 (case 1).—Graphic chart. *A* indicates the time at which cystoscopy was done; *B*, transfusion of blood; *C*, axillary temperature; *D*, operation.

infiltration near the midline, but since the stomach was well walled off and the gastrohepatic omentum seemed infiltrated and approximated close to the under surface of the liver, no effort was made to break up these adhesions.

The liver was aspirated but pus was not found.

The finger was introduced in the foramen of Winslow, and I could feel nothing pathologic.

The operation did not add any positive diagnostic information. A transfusion was done at the same time.

In spite of repeated transfusions and infusions, which were done prior to the final exploratory operation, the patient grew steadily worse and died several days after operation without sufficient evidence having been found to make any one of the many surgeons, internists and urologists who saw the patient even suspect the real nature of the disease.

The critic who may be inclined to wonder why so much discussion is indulged in before the presentation of the autopsy record can be answered by the outstanding fact that of such men as Matas, C. Jeff Miller, Hume, Lemann, Burns, Pratt and others who saw this case in consultation with me, not one suspected the true status. If this is true, then others may do well to ponder over this history that they may profit, if they can, by this sad experience. Had we known the diagnosis, it is true that nothing would have been of value; in fact, we might have been less hopeful earlier in the case.

The outstanding autopsy observation included large retroperitoneal glands in the vicinity of the stomach, pancreas and duodenum, and an ulcerating lesion of the wall of the stomach. All of the lesions were reported by Dr. Lanford to be "lymphoblastoma of the lymphosarcoma type" (fig. 2).

On reviewing these tissues at a later date at my request, Dr. Lanford reported that they were lymphoblastoma of the Hodgkin's type. Specimens of this tissue were sent to Dr. Bloodgood for examination. Because of Dr. Bloodgood's absence, Dr. L. Clarence Cohn had sections made, and his report is here appended. "Microscopic section showed no germinal centers, no remains of lymphoid architecture, a very cellular tumor, little more stroma than in case 2 (Miss A.), and many large cells of the Dorothy Reed type. I am inclined to think we are dealing with Hodgkin's disease."

Autopsy revealed then a retroperitoneal lymphoblastoma of Hodgkin's disease. There was nothing on which to base such a diagnosis clinically unless one suspects every case of unexplained fever, and that would hardly be justified.

Comment.—When the clinical picture is compared with the implied significance of the original laboratory report a contradiction is noted. The clinical picture was certainly that of an infection, so much so that each one who was consulted in the case sought a source from which the infection could have originated. Closer scrutiny of the laboratory report, if interpreted in the light of recent discussions in the literature, may help. Again, it may add to the confusion as there are certain terms that have been used interchangeably by some authors when discussing diseases of lymphoid structures.

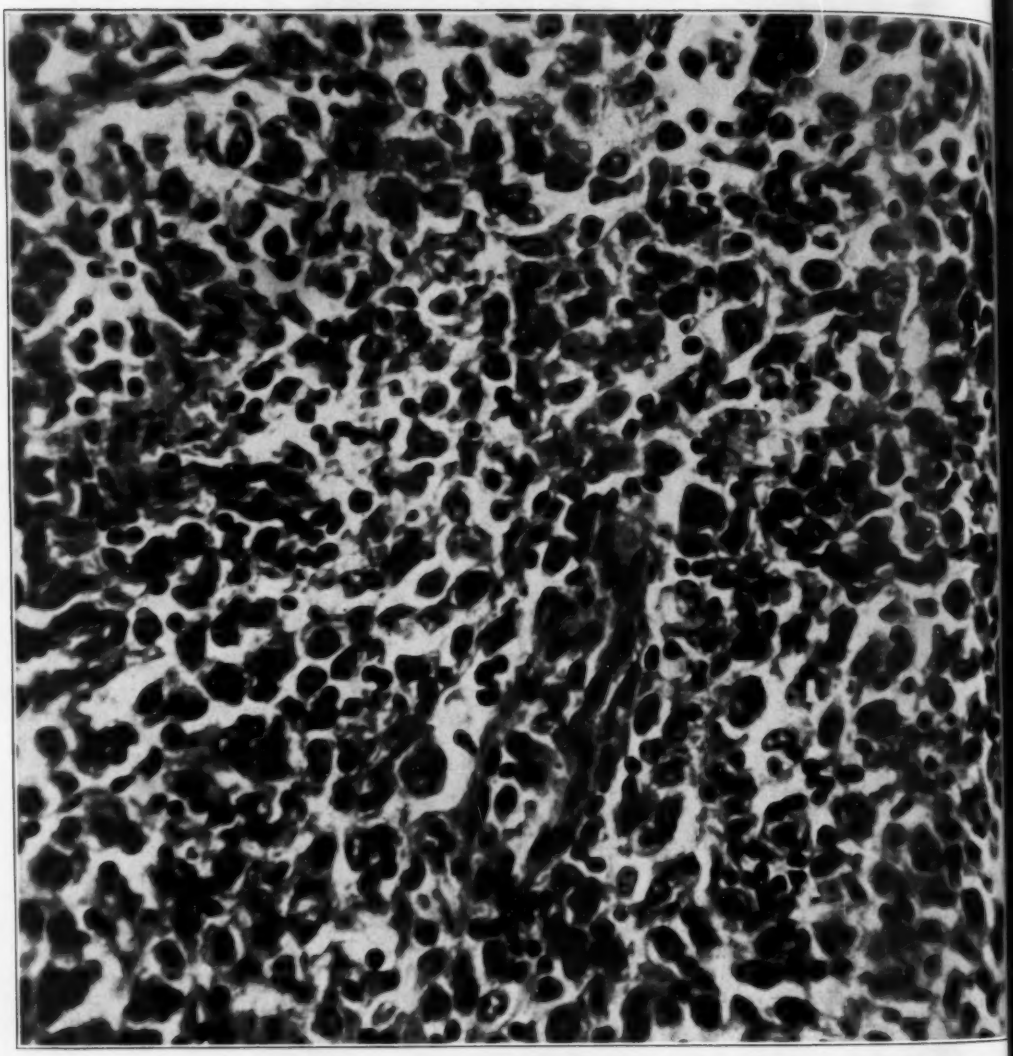

Fig. 2 (Case 1).—Photomicrograph of a section of the tumor. The diagnosis made by Dr. John Lanford was lymphoblastoma of Hodgkin's type; by Dr. L. Clarence Cohn, Hodgkin's disease.

Minot and Isaacs remind one:

> Classification leads to clarification and yet confusion arises from sharp distinctions between conditions that have many resemblances; which may be because some of the conditions are but different phases of the same disease. This is the state of affairs for those disorders that may be placed under the same general heading of lymphoblastoma.

It is not the purpose to differentiate here the causative factors that produce retroperitoneal tumors, but simply to direct attention to the presence of such observations. Whether lymphoblastoma, lymphogranulomatosis, Hodgkin's disease or lymphosarcoma are responsible for the glandular involvement is for the moment not my primary consideration, yet one cannot proceed without discussing some of the interesting phases of lymphoblastoma which have been recently discussed in the literature.

From foreign countries, as well as from our own country, there seems to be a general tendency to suggest again that lymphoblastoma or lymphogranuloma is an infection and not a malignant disease in the ordinary accepted significance of the term.

In 1926, Curtis Burnam stated:

> The disease presents the earmarks of a chronic infection, the neoplastic nature of the disease has been almost abandoned and is very rarely referred to in the literature.

Again in 1928, Burnam stated:

> While it is true lymphosarcoma is a neoplastic, Hodgkin's disease is an infection in all probability.
>
> In acute Hodgkin's disease the general symptoms may completely mask the picture; this is especially true in the abdominal and intestinal type—to such an extent that no gland can be found on clinical examination. It is not uncommon to meet with patients who have had radiotherapy and who present no glandular enlargements and yet show the fever, the weakness, the skin manifestations and other symptoms of the disease. In most instances the active trouble is in the retroperitoneal glands, and the failure to find tumor is due solely to our imperfect methods of investigation.
>
> Fever of an irregular type, both as to daily variations and periodicity, is quite common in Hodgkin's disease and is absent in lymphosarcoma except in the last stages. The high intermittent fever, sometimes reaching a peak of 106 F., and accompanied by chills, and sweats, is particularly distressing. Occasionally in general and frequently in intestinal cases the picture suggests typhoid fever.

In 1929, Ayrosa and Pessoa found a corynebacterium in the cultures from histologically verified cases of Hodgkin's disease, thus adding the weight of their investigations to the theory that Hodgkin's disease is an infection.

Nee and Cailliau, in 1929, stated:

> Lymphogranulomatosis is truly an infectious process. The disease has neither the anatomo-clinical appearance nor the histological substratum of cancer; its pseudo-metastases are not destructive like those of cancer and they have all the characteristics of an infectious dissemination.

Does not the quotation from Burnam describe fully the reason for our failure to evaluate correctly the symptoms and arrive at a proximate diagnosis?

While the present case report does not justify a conclusion, such an experience when interpreted in the light of the current literature leads one to an impression that lymphoblastoma, lymphogranuloma or Hodgkin's disease (if those terms are synonymous, and they seem to be accepted as such) is an infection. The fact that this disease is eventually fatal is not necessarily an argument against an infection.

Minot and Isaacs expressed the belief that "one of the big problems of modern medicine is to unravel the nature of the group of conditions that have progressive enlargement of the lymphoid tissue as their most prominent features."

I leave further discussion and elucidation of this subject to those more competent to answer the problems.

The clinical problems are of interest. How long the glandular involvement had been present and what part of the symptoms their presence was responsible for cannot be answered. It is humbling to realize that diagnostic measures during life were not of value, and even the observations made at autopsy are not conclusive.

Such a case as the one reported makes it desirable for one to study with care the clinical manifestations in those cases in which there is known to be retroperitoneal masses with a view to see whether a characteristic syndrome exists. After such a study, I have not been able to find such a syndrome.

RETROPERITONEAL LYMPHOSARCOMA; CHYLOTHORAX

Though case 2 will be reported in detail elsewhere, a summary of it will be included in this presentation because the clinical and pathologic pictures were confused at times with Hodgkin's disease and because the retroperitoneal mass produced obstructive phenomena, ascites, which was at first serous and later chylous, chylothorax and edema of the extremities.

> CASE 2.—A woman, 46 years of age, first noticed an enlargement of the glands in her neck one year before she came to the infirmary. During the next twelve months, the axillary, inguinal and epitrochlear glands successively became enlarged. The masses in the glands were discrete and painless. The disease ran an irregular febrile course. There was progressive loss of weight, digestive disturbances,

orthopnea, nausea and vomiting, progressive enlargement of the abdomen and extreme weakness. At the first examination, a diagnosis of Hodgkin's disease was suggested.

The patient was admitted to Touro Infirmary for diagnostic study. The Wassermann reaction of the blood proved to be negative. Other examinations of the blood revealed a secondary anemia, without a leukocytosis and without a marked variation from the normal differential leukocyte count. So far, the results of the examinations seemed to eliminate the diagnoses of lymphatic leukemia, tuberculosis and syphilis. A biopsy was done, and lymphoblastoma not characteristic of Hodgkin's disease was reported.

As the condition progressed, it was necessary to do repeated paracenteses and thoracenteses. The fluid removed from the chest was of a milky consistency, and the analysis of this showed it to contain about 1 per cent of fat. A total of

Fig. 3 (Case 2).—Roentgenogram of the chest. In this case a diagnosis was made of retroperitoneal and mediastinal lymphosarcoma; chylothorax and chylous ascites.

nearly 12,000 cc. of chylous fluid was evacuated from the two pleural cavities during the course of the disease (fig. 3).

At autopsy, enlarged tumors of the lymph gland were found in the mediastinum which in some instances were about the size of an English walnut.

The retroperitoneal lymph nodes were enlarged and matted together and on following up the thoracic duct enlarged structures resembling tumor masses were found at intervals along its entire course which were pressing on it preventing the free flow of fluid.

The broad ligaments of the pelvis were filled with firm, hard nodules, varying in size from that of a small pea to that of a pecan, and which were secondary growths. The tubes presented similar nodules. The uterus was also nodular, presenting secondary growths on its serous surface. The right and left ovaries were infiltrated with secondary growths.

The spleen was about 1 by 10 by 5 inches (2.5 by 25.4 by 12.7 cm.). The cut surface showed that the normal tissues had been largely replaced by new growth, and the appearance of the spleen was somewhat like that of a cross-section of a bologna sausage.

The right kidney contained small secondary growths.

The anatomic diagnosis reported by Dr. Lanford was lymphosarcoma, primarily in the retroperitoneal lymph nodes, with secondary metastasis to the lymph adenomatous structures of the entire body; secondary lymphosarcoma of the kidney, and lymphosarcoma of the spleen.

Blocks of the mediastinal glands and of the spleen were submitted to Dr. Ewing and Dr. Bloodgood.

Dr. Ewing reported on October 6, 1930: "I think that this is a case of lymphosarcoma. Whether it arises on the bases of Hodgkin's disease, as Dr. Stewart thinks, I am unable to state, but I do not find any definite lesions of Hodgkin's disease" (fig. 4).

A specimen was sent to Dr. Joseph Bloodgood. During his absence his associate, Dr. Clarence Cohn reported the following: "Microscopically, the section from the gland showed a lymph gland in which there was no germinal centers. The gland was very cellular and there was a great deal less stroma than we usually see in Hodgkin's disease. It was more like the gland of lymphosarcoma. Nevertheless, there were so many large cells with multiple nuclei suggesting Dorothy Reed cells that I would be more inclined to think of Hodgkin's disease than lymphosarcoma. Section from the spleen showed pretty much the same picture except perhaps there was a little more stroma and not so many of the large multinucleated cells. Nevertheless they were present."

Comment.—The retroperitoneal growths in this case were large enough and so located that they produced obstructive phenomena; in another case, which will be described (case 4), there was a larger mass which did not produce edema or ascites. The mass in this case was located on the left side.

In spite of the large size of the retroperitoneal masses, digestive disturbances were late manifestations in the case of Miss A. (case 2); therefore, the size of the mass is not a determining factor in the production of this symptom. Location near the celiac plexus may be a factor; such is suggested in the first case of this series.

Though the clinical syndrome and the tissues grossly were totally different, there existed confusion in the pathologic changes as well as the clinical diagnosis.

In view of the difficulty which most distinguished pathologists have in arriving at a definite diagnosis, there is some excuse for this case having been considered Hodgkin's disease during life.

RETROPERITONEAL SARCOMA; SARCOMA OF THE THIGH

The next case to be presented is one in which a known retroperitoneal mass existed. This tumor was apparently secondary to a sarcoma on the outer side of the thigh.

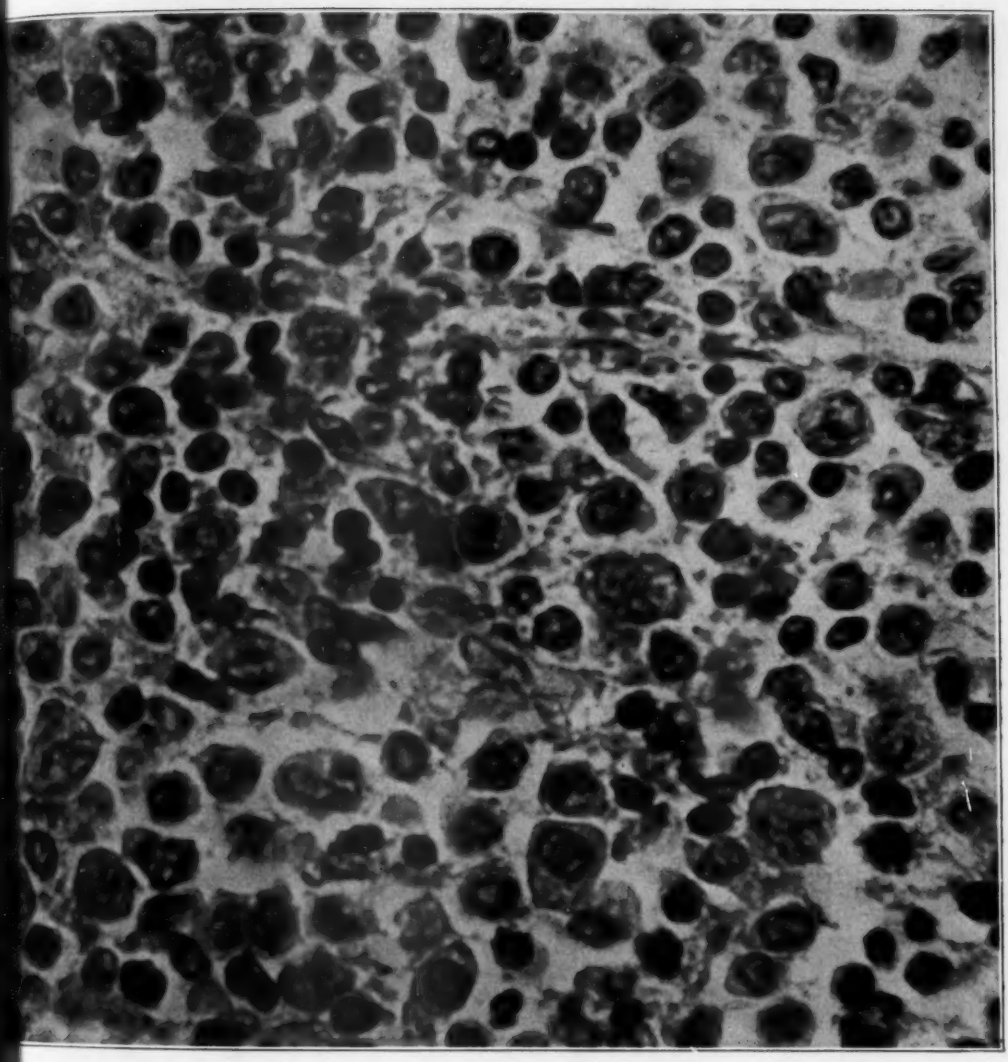

Fig. 4 (case 2).—Photomicrograph of a section of the tumor. The diagnosis made by Dr. John Lanford was lymphosarcoma; by Dr. James Ewing, lymphosarcoma; Dr. L. Clarence Cohn was more inclined to think of Hodgkin's disease than lymphosarcoma.

The following report is taken from a record of the history of Touro Infirmary:

CASE 3.—Mr. J. L., aged 50, was admitted to the infirmary on Jan. 6, 1925, with a diagnosis of lymphosarcoma of the right thigh with retroperitoneal metastasis. The growth on the thigh was excised with the radioknife, and deep roentgen therapy was instituted for the retroperitoneal involvement.

About five months before admission to the infirmary, the patient noticed a mass on the right buttock which rapidly increased in size; at the same time he noticed a swelling in the groin. Other masses had not been found by the patient.

He did not think that he had lost weight; his appetite was fair; there were no digestive discomforts, except that he suffered from constipation.

Physical examination revealed a fairly well developed and well nourished man. The neck was normal. In the right inguinal region there was a mass of glands which was elevated, hard and painful to the touch, and probably deep. Above the brim of the pelvis one got the impression of a retroperitoneal mass. The inguinal glands on the left side were palpable. The liver and spleen were not palpable.

The entire right lower extremity was larger than the left.

Rectal examination revealed a mass on the right side.

On the right thigh there was a mass about 10 by 5 cm., fairly hard, smooth and apparently encapsulated. The overlying skin was soft and freely movable over the mass. There was limitation of motion of the right knee and hip. Flexion of the knee beyond a right angle was painful.

A roentgenogram of the pelvis and chest, on Jan. 7, 1925, did not reveal any evidence of a pathologic process within the chest, except a marked fibrosis throughout both lungs. Metastases to the bone was not found in the pelvis.

The diagnosis of retroperitoneal lymphosarcoma was made for the following reasons:

The question of lymphatic leukemia seemed to be eliminated because of the blood picture which showed a total of 11,500 white cells and of these only 21 per cent were lymphocytes. There was a negative Wassermann reaction, and the question of carcinoma was considered, but there was no primary lesion which we could find that might be considered epithelial in character. A barium sulphate enema did not show any evidence of an obstructive lesion in the rectum or sigmoid colon.

Primary carcinoma of the lymph gland was considered, but on account of its rarity we felt that there was no reason to venture this diagnosis. Hodgkin's disease was considered. The length of time that the disease had remained limited to the inguinal and iliac glands made a diagnosis of Hodgkin's disease unlikely, yet we felt that it was not possible to eliminate it without section of one of the glands. The mass on the thigh and the finding of the glands suggested that we were dealing with lymphosarcoma. Operation confirmed this impression.

In January, 1925, the growth on the thigh was circumscribed and removed with a radioknife. The growth was still encapsulated; it had not invaded the surrounding muscle tissue from which it was readily separated. The growth presented multiple nodulations on its surface, and through the thin capsule it had a gray mottled appearance. The interesting feature of the whole procedure was the lack of burning from the radioknife. (This note was made five and one-half years ago when electrosurgery was a new method in my hands.) After removal of the growth, the wound was sutured with interrupted silkworm suture. On section, the growth presented grossly the appearance of a lymphosarcoma.

According to a laboratory report made by Dr. Lanford, the mass was light gray to light yellow in color, firm in consistency and was composed of large

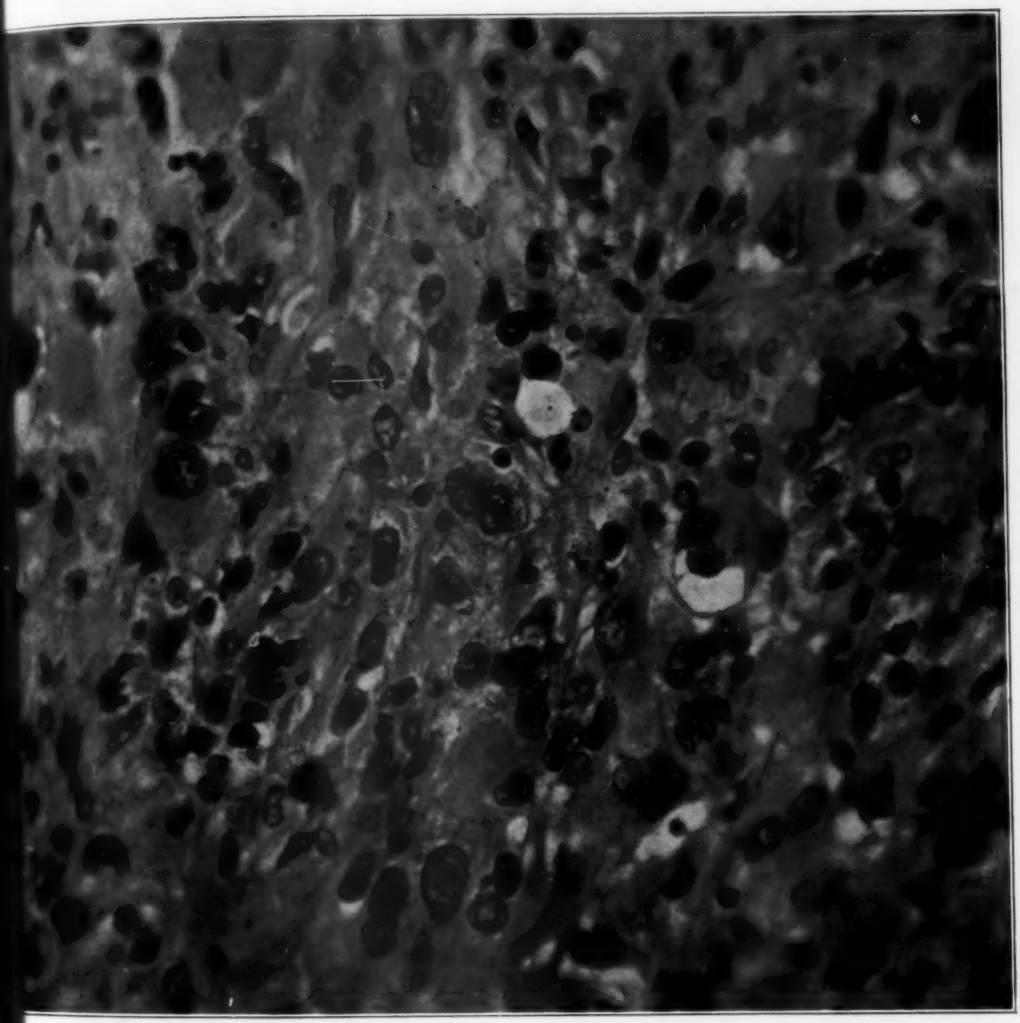

Fig. 5 (Case 3).—Photomicrograph of a section of the tumor. A diagnosis of retroperitoneal sarcoma was made.

nodules measuring about 2 cm. in diameter. Surrounding the connective tissue, there were a large number of blood vessels. A diagnosis of mixed cell sarcoma was made (fig. 5).

The postoperative treatment consisted of deep roentgen therapy and erysipelas and prodigiosus toxins (Coley's).

On February 23, there was no apparent diminution in the size of the retroperitoneal mass.

The patient was readmitted to the hospital on April 16, 1925, at which time he was scarcely able to walk. Beneath the old scar on the right buttock there was a firm circumscribed mass which was "fixed" to the deep structures, though not adherent nor a part of the bone.

Examination on April 16 showed a firm, painful swelling in the right inguinal region which extended down over the ileum from above the pelvic brim. Masses were felt in the abdomen as before. The right leg was larger than the left. There was no evidence of pulmonary or cardiac pathologic processes.

A report on June 8 showed that for the past month the patient had steadily grown weaker, and his pain had become more severe. His leg became more and more edematous until it was about twice its normal size; the scrotum also was markedly edematous and there was evidence of fluid in the abdomen. He was getting over 24 minims of erysipelas and prodigiosus toxin (Coley's) with no reaction.

A roentgenogram of the chest taken on June 10 revealed evidence of a large metastasis in the lower lobe of the left lung with a beginning metastasis in the upper right side.

The edema of the extremities and respiratory distress progressively increased, and the patient died on June 16.

On opening the abdomen at autopsy, about 4 liters of fluid were found. The peritoneum was smooth and glistening. In the mesentery a number of large, irregularly lobulated nodules were found. The pelvis was filled with a large, irregular, lobulated mass which had invaded the ileum. The large bowel had been infiltrated by the growth.

The lymph nodes of the hilus of the left lung showed several large masses such as were described in the mesentery. On the pleura, at the posterior axillary line on the left, there were three cystic masses varying from 2 to 10 cm. in width. These infiltrated the ribs. The spleen was small and firm, and the surface was rough. There were small areas of involvement in the liver varying in size.

The anatomic observations were: sarcoma, primary origin unknown, involving the pelvis and the entire gastro-intestinal tract, the liver, the lungs, the pleura, the kidneys and the lumbar vertebrae.

Microscopic examination by Dr. Lanford showed mixed cell sarcoma.

In Dr. Bloodgood's absence, Dr. L. Clarence Cohn, his associate, reported the following: "In this section we found a good deal of stroma, which took a faint stain, and a tumor chiefly of the small round and spindle cell type. It was much different from the tumor of the testicle. The cells did not suggest the cells of a malignant mole. Here and there were multinucleated giant cells. The tumor was not of the lymph gland type. I would be inclined to think the tumor was primary, a sarcoma originating in a bursa, or tumor of a nerve sheath. In a number of cases sarcoma metastasized to the glands."

The outstanding features of this case were: (1) a growth on the outer side of the right thigh; (2) a metastatic retroperitoneal growth; (3) recurrence of the growth on the right thigh; (4) edema of the right leg and scrotum; (5) ascites; (6) late metastasis to the lungs; (7) failure of the roentgenogram to aid in the diagnosis even though an opaque enema was given.

Comment.—All of the evidence of a retroperitoneal tumor presented by this case were late manifestations, and may be attributed to pressure. Such late evidence can hardly be counted on to aid a patient who has a growth sufficiently small to be removed surgically.

RETROPERITONEAL SARCOMA WITHOUT METASTASES

CASE 4.—J. P., a colored man, aged 51, was first seen at Touro Infirmary in the gastro-intestinal clinic on Feb. 2, 1930, at which time he complained of pain in the epigastrium, vomiting, indigestion, belching and constipation. About one month before coming to the clinic he began to suffer with pain in the epigastrium, sometimes extending to the back. After meals he had a feeling of fulness in the stomach which was relieved by belching and vomiting. This vomiting occurred about thirty minutes after meals. The pain in the epigastrium, however, did not seem to have any reference to meals. The patient's appetite was fairly good, but he forced himself to eat because he had lost 22 pounds (10 Kg.) during the last month.

Physical examination showed a well developed, fairly well nourished man, apparently not in any pain and not sick.

The ribs were prominent with sunken interspaces. There was depression and flaring of the lower ribs on the left side. Percussion was hyperresonant. The heart was difficult to outline, but the heart sounds were clear. The breath sounds were distant.

The abdomen was slightly distended, and there was some rigidity on the left side. There was a mass about 4 inches (10.16 cm.) in width and projecting from beneath the ribs on this side. The mass was firm and smooth, dull on percussion and occupied about the same position as an enlarged spleen. The mass was movable on deep inspiration. The liver was not palpable, the upper border of it being at the sixth rib.

The genitals were normal.

On February 2, a test breakfast revealed the quantity to be 50 cc., chymification, good; hydrochloric acid, 22; total acidity, 44.

The patient complained of rather acute pain in the left lumbar region. On aspiration of this region with a 21 gage needle, a small amount of serosanguinous fluid was obtained. The tumor mass was apparently fluctuant.

On February 27, examination showed that the mass was apparently enlarging fast enough to be perceptible from day to day. Enlargement of the spleen was suggested by a superficial mass with a rounded edge, moving with respiration, projecting from under the left ninth rib, and having a smooth surface. There was a projecting mass in the loin with dulness and apparent fluctuation, suggesting the kidney. The genito-urinary department found general enlargement of the prostate. Stasis was not noted in either kidney. The Wassermann reaction was negative. The feces and urine were negative.

Roentgen examination reported by Dr. Henderson (fig. 6) revealed the following: The kidney on the right side was not identifiable, but an opaque catheter was passed up into the pelvis of this kidney. On the left, the ureter passed upward to the upper level of the sacro-iliac synchondrosis, from which point it passed inward to rest anterior to the spine. The pelvis of the kidney was resting anterior to the spinal shadow, and was exhibiting hydronephrosis. Lying to the left side of the kidney was a large retroperitoneal mass which was not springing from the kidney, but was displacing the kidney by pressure. Aside from the hydronephrosis visible, evidence of a pathologic process could not be made out in the

kidney, ureter and bladder, and the type of mass which was displacing this kidney could not be definitely determined. Retroperitoneal sarcoma, however, must be considered as most likely.

On March 3, following a barium sulphate enema (fig. 7), roentgen examination was done. Dr. Henderson made the following report: There was a complete lack of haustral markings in the distal transverse and entire descending colon. This had been converted into a smooth wall tube, and a moderate amount of dilatation had occurred. In addition, there was an alteration in the general distribution of this bowel, the transverse colon resting far down in the pelvis, the splenic flexure resting unusually high up, and there was an alteration of its normal geographic location which was believed to have been occasioned by some rotation.

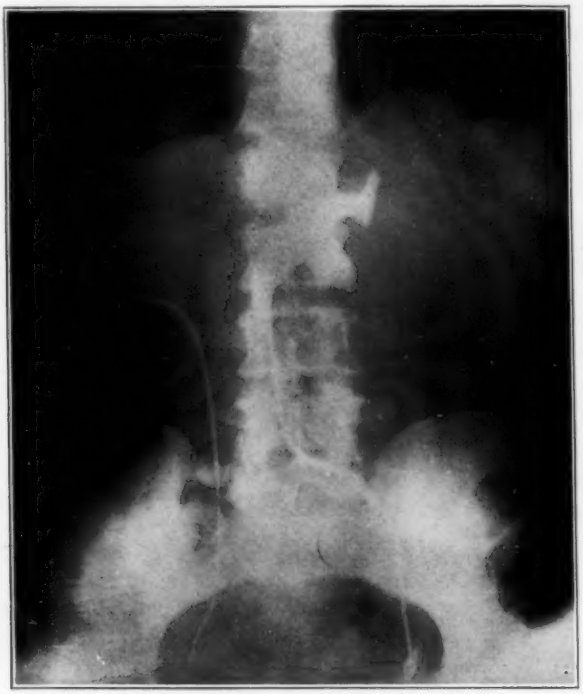

Fig. 6 (Case 4).—Roentgenogram after pyelography.

In the distal transverse colon about 10 cm. proximal to the splenic flexure an infiltrative lesion could be observed in the wall of the bowel which was partly narrowing and constricting this, but from one side only. The infiltrative type of lesion, the lack of complete encircling of the colon and the alteration in the haustral markings distal to the lesion placed this in the inflammatory class.

On March 11, I noted that the left side of the abdomen and the axillary region presented a number of small pigmented areas. There was a loss of symmetry in the chest. The lower costal margin was elevated sharply at the seventh rib. This caused the costal margin on the left to be above the right side. There was a bulging in the left lumbar region. The left side of the abdomen was distinctly more prominent than the right side which seemed to be retracted and soft; there was some rigidity in the upper segment. Below the umbilicus on the

left side the abdomen was soft; above the umbilicus there was a hard nodular movable mass the edge of which was distinctly palpable about 1½ inches below the costal margin. There was a circumscribed bulging in the left posterior scapular line but no fulness at the costovertebral angle. I suggested a fluoroscopic examination to see if the diaphragm was elevated on the left side, and if the mass moved; also a complete examination of the blood. I believe that the mass was the spleen, but just what the nature of the splenic enlargement was and what the underlying cause remained to be determined.

On March 17, the platelet count showed 275,000 platelets per cubic millimeter (Liles). Examination of the blood showed: total red cells, 3,460,000; hemoglobin, 70 per cent; color index, 1; total white count, 13,500; small lymphocytes, 19; large lymphocytes, 0; neutrophils, 81; eosinophils, 0; basophils, 0.

Fig. 7 (Case 4).—Roentgenogram taken after a test meal of barium sulphate. A diagnosis of retroperitoneal sarcoma was made.

Operation was performed on March 10. The preoperative diagnosis was: (1) splenomegaly of unknown origin and (2) retroperitoneal sarcoma; the postoperative diagnosis: inoperable retroperitoneal sarcoma.

An incision was made in the left rectus muscle. Free fluid was not found in the peritoneal cavity. A large lobulated mass was found occupying the entire left side of the abdomen with the bowel overriding and closely attached to the lateral wall. The stomach was adherent to the right side of the mass. The vessels which covered the mass were greatly dilated. The glands in the mesentery were a reddish color and looked like large "dots" on a veil. Exploration revealed a small spleen riding on top of the mass, which was fixed posteriorly to the abdominal wall. It was decided to remove only a small gland. The liver was large, but

there was no evidence of metastasis to the liver. After examination, we felt that any further procedure would result fatally.

Autopsy was performed on August 9. The body was that of a well developed, poorly nourished Negro man measuring about 5 feet, 10 inches (177.8 cm.) and weighing about 115 pounds (52.1 Kg.). The trunk was distorted by a large tumor mass situated on the left side which had pushed up the lower portion of the thoracic cavity and partly obliterated the left peritoneal cavity. There was a healed surgical scar over this area.

The left abdominal cavity was largely obliterated, being entirely occupied by a tumor mass which was covered by the peritoneum and had pushed the intestines to the right and elevated the left thoracic wall. The splenic flexure and descending colon and also the pancreas and the spleen were adherent to the peritoneum over the tumor mass.

The lungs for the most part were crepitant throughout and grayish, and contained many areas of black pigment. The apex of both lungs showed scar tissue, and in the left lung were a number of irregular areas showing caseation, some of which show deposits of lime salts. Evidence of new growth either in the mediastinum or in either lung was not found.

The liver was rather small and firm and slightly nutmeg in appearance.

The gallbladder contained a small amount of bile but was not distorted.

The spleen did not show any evidence of a growth.

The right suprarenal gland was normal and the left was encapsulated in the tissue around the tumor mass and showed no gross evidence of a pathologic process.

The right kidney was covered with fairly adherent perirenal tissue containing some fluid. It was not increased in size and on section showed a normal contrast between the cortex and medulla. The left kidney was encapsulated in the new growth.

The new growth was rather oval in shape measuring about 15 inches (37.54 cm.) in one diameter and 12 inches (30.48 cm.) in the other. It was situated entirely in the retroperitoneal space and was adherent to the peritoneum, the diaphragm and the posterior and lateral abdominal walls and had partly infiltrated into the posterior border of the kidney while over its anterior surface was stretched the suprarenal and pancreas, the splenic flexure of the colon and sigmoid, and the spleen. The tumor was of a brainlike appearance, and the consistency of the whole mass was semifluctuating. On sectioning, it offered no increased resistance to the knife and presented a cut surface that resembled very much that of the brain, being relatively uniform and showing a number of areas of necrosis. Some of the necrotic areas had liquefied.

Anatomic diagnosis made by Dr. Lanford was retroperitoneal sarcoma (fig. 8).

Dr. L. Clarence Cohn, associate of Dr. Joseph Bloodgood, during the latter's absence, reported the following: "Here the stroma predominated; to express it in other words, there was a great deal more of intercellular substance. The cells again were of the large round type. This section did not suggest Hodgkin's disease or lymphosarcoma, but rather a primary retroperitoneal sarcoma not of the lymphosarcoma type, but more like a fascial sarcoma."

The outstanding features of this case were: 1. A large mass was found in the left side of the abdomen which was movable with respiration. 2. Preoperatively the clinical diagnosis of a splenomegaly of undetermined origin seemed likely. 3. Epigastric symptoms caused the patient to come under observation. 4. Roentgen diagnosis proved to be the most accurate preoperative evidence which we had. 5. Emaciation was progressive. 6. At autopsy, there were no metastases to lymph glands or other organs. 7. There were no ascites. 8. Edema of the extremities

Fig. 8 (Case 4).—Roentgenogram of a section of the tumor. The diagnosis made by Dr. John Lanford was retroperitoneal sarcoma; the same diagnosis was made by Dr. L. Clarence Cohn.

was not present. The lack of edema may easily be explained by the fact that the mass was on the left side and did not interfere in any way with the lymph or venous return.

TERATOMA OF TESTICLE; RETROPERITONEAL METASTASES

In the following case of retroperitoneal metastases from an original teratoma of the testicle, the patient presented as the outstanding disturbance digestive symptoms for which he was referred by the urologist who operated on him originally to Dr. S. K. Simon, a gastro-enterologist. It was through the courtesy of Dr. Simon that I had the opportunity to see this patient.

In order to do justice to many interesting features of the case, an outline of the history will be appended and a discussion of other cases of teratoma in which results were more fortunate will be included.

Three cases of teratoma of the testicle have come under my observations. In one, operation had been done nine months before, and a retroperitoneal metastasis had already developed. I performed the operation in two cases, and the patients are living and apparently well five and two years after operation, respectively.

The case with metastases is of interest, especially in connection with other cases included in this report. The other two are of interest because of the apparently excellent outlook to date. The general topic of teratoma will not be gone into in detail because there are so many excellent reports of large series by Hinman, Coley, Dean, Tanner, Chevasau and others.

In view of the statement of Tanner, that the average mortality based on four years postoperative period was 80 per cent, cases in which the patients survive that period should be recorded.

CASE 5.—Mr. O. R., aged 32, was admitted to Touro Infirmary on Sept. 23, 1925, to the service of Dr. S. K. Simon. The patient's chief complaint was pain in the lower part of the abdomen. In January, 1925, he had been operated on for teratoma of the testicle. In June, 1925, he began to lose weight. During the two months preceding his admission to the hospital, he had lost 25 pounds (11.3 Kg.). His weakness had been progressive, and at the time of his admission was extreme.

About twenty minutes after taking food he would be nauseated and vomit for relief. This progressed to the point that he could hardly retain any food. The abdominal pain was sharp and was located particularly in the left lower quadrant. The patient noticed a mass in his abdomen, for the treatment of which deep roentgen therapy was instituted.

The notes from his record state at the time of his admission that he was fairly well developed but poorly nourished. Examination of the glandular system showed the cervical, epitrochlear and inguinal glands palpable, but not enlarged. Examination of the chest failed to reveal evidence of an intrathoracic pathologic process. The abdomen was flat, symmetrical and muscular. A mass the size of a lemon just to the left of the vertebral column was palpable. The mass seemed to be slightly movable, and it was noted that it apparently had deep attachments.

During the time that the patient was under the observation of Dr. Simon on the gastro-intestinal service from September 23 to October 16, a gastro-intestinal series and other clinical investigations were done to determine if there was any intrinsic gastric lesion. The roentgen report made on November 4 by Dr. Henderson was extremely interesting. The chest showed no evidence of metastatic involvement or other pathologic process. The stomach filled quite well, with no intrinsic filling defects. The peristalsis and motility were considered normal. The stomach itself was quite large and atonic. The pylorus was freely patent, and the food, by manipulation, could be forced through the pylorus along the bulb quite well. The second portion of the duodenum described a wide circle and was markedly dilated and as the food arrived at the lower portion, evidence of obstruction was observed, the meal banking up at this location and being regurgitated into the stomach. An impression was gained of an extrinsic pressure. The six hour observation showed the stomach retaining approximately one-half the meal with no barium sulphate in the small bowel. The twenty-four hour observation showed the meal in the ascending and proximal transverse colon; no filling defect was observed, and the transverse colon was lying well down in the pelvis. The thirty hour observation showed the meal largely having passed from the body, some islands of barium sulphate still remaining in the ascending colon and the proximal transverse colon.

The conclusions made were that there was no pathologic process intrinsic to the gastro-intestinal tube. The stomach was atonic and dilated. The obstruction at the second portion of the duodenum was considered external (fig. 9).

The roentgen observations are of particular significance from a diagnostic standpoint. While one might not be so fortunate as to find such definite evidence of extrinsic causes for obstruction in other obscure cases of abdominal disease, such an investigation should not be overlooked.

During this period the patient also complained of pain after eating, which at times radiated to his scapula. At times he had hiccups. There was no gastric retention.

On October 16, the patient was referred to me for surgical consultation and the following was noted: The abdomen was soft in the lower segments. The inguinal glands were not enlarged. The iliac group could not be palpated through the abdominal wall on either side. Rectal examination did not reveal any mass of retroperitoneal glands. To the left of the vertebral column on a line with the umbilicus, there was a firm mass approximately 4 by 2 cm. which was nodular and freely movable.

Before recommending erysipelas and prodigiosus toxins (Coley's) or massive radiation therapy, we wanted to see some roentgenograms. Presumptive evidence suggested metastasis, yet the mobility of the mass made one hesitate to make such a diagnosis. In view of the foregoing evidence, I believed an exploratory laparotomy to be indicated.

On October 21, the following operation was done: A high paramedian incision was made on the left side, and the rectus sheath opened; the rectus muscle was retracted outward. When the peritoneum was opened, the stomach was found to be normal and the pylorus patulous; the gallbladder was soft, translucent and emptied easily. The liver was smooth. No adhesions were found.

On the left of the umbilicus and below it lying on the aorta, behind the peritoneum, there was a chain of movable nodular masses; they were of unequal size, the largest being about 1 inch (2.5 cm.) in diameter. These masses moved

with the pulsations of the aorta. The lower limit of the palpable masses was the bifurcation of the aorta. It was evident then that the condition was a metastatic growth in the lumbar lymph nodes, following teratoma of the left testicle. I did not feel justified in attempting to remove them.

On November 2, the administration of Coley's toxins was started. The first reaction was noted November 10. The patient continued under treatment, and the mass apparently diminished in size. He was discharged from the hospital on November 14 to return to the clinic for the administration of the toxins.

On July 19, 1926, he was readmitted to the hospital. In the interim he had lost weight. He was very weak and his general appearance was that of a severe

Fig. 9 (Case 5).—Roentgenogram of the stomach and duodenum after a test meal of barium sulphate. According to Dr. Henderson's report the second portion of the duodenum described a wide circle and was markedly dilated; as the food arrived at the portion, evidence of obstruction was observed, the meal banking up at this location and being regurgitated into the stomach. From this, the impression was gained of an extrinsic pressure. A diagnosis was offered of retroperitoneal metastasis from teratoma of the testicle.

secondary anemia. On examination, we found a mass the size of a hen's egg located above the clavicle to the left of the sternoclavicular junction. This evidently was a metastasis to Ewald's gland. There was a history of light-colored stools, nausea and vomiting. There was a palpable mass about the size of a hen's egg just above and to the right of the umbilicus. The mass did not give the impression of being attached to the liver, but seemed to be connected with some structure below the liver.

Dulness was found posteriorly over a triangle having its vertex in the midline about the level of the lower angle of the scapula and its base about the level of the costal margins. The breath sounds and fremitus were diminished over this area.

There was a faint diastolic murmur over the third space at the left border of the sternum, and slight enlargement of the heart downward.

At this time another 5,400 mg. hours of radiation was given over the mass in the epigastrium.

Roentgen examination, made by Dr. Henderson, showed that the diaphragm was smoothly contoured; the cardiac and great vessel shadows were not increased: the thoracic cage was bilaterally symmetrical. The pulmonary fields were free from metastasis or other types of lesions. An observation of unusual interest was that a large oval shadow was observed behind the heart overlying the spine; the exact nature of this could not be determined from the roentgenogram of the chest. and it was recommended that this patient return for further study.

It was finally decided that this was a mediastinal growth as fluoroscopy failed to reveal an expansile pulsation in the mass.

The patient was again admitted to the hospital on September 11, at which time radium was applied to the abdomen, 5,400 mg. hours. The supraclavicular glands were still enlarged. The patient was discharged on October 4 and died November 7 at the Charity Hospital. The family refused to grant permission for autopsy.

Case 6.—Mr. J. B., a white man, aged 28, during April, 1925, noticed an enlargement of the left testicle. There was no history of either an injury or venereal infection. After consulting several surgeons, the patient came under my observation.

On initial examination, I found that the left testicle was about 2½ inches (6.27 cm.) in its long axis. It was hard and freely movable; the epididymis was not enlarged, and the testicle was not adherent to the scrotum. Palpation did not cause pain.

Operation was performed on May 1. An incision was made over the upper portion of the scrotum and the inguinal canal. As soon as the tunica was incised, about 1½ ounces of translucent bloody fluid was evacuated. The tumor was about 2 inches (5 cm.) in length, elliptical and solid; the epididymis was closely adherent to the testis. Nodules could not be palpated in the globus major or minor. The testicle was smooth and had a grayish appearance. The aponeurosis of the external oblique was split, and the vas followed up to the internal ring, ligated high, then dropped back. The spermatic vessels were ligated high. No glands were palpable in the retroperitoneal space. A specimen was given to Dr. Lanford for rush diagnosis and study. He reported at the table a highly cellular growth but was not able to state the exact nature of the tumor.

The laboratory report made by Dr. Lanford follows: The specimen consisted of the testicle, epididymis, vas deferens and surrounding tissue, and tunica vaginalis. The testis measured 6 cm. in length and 4 by 3 cm. It was covered by a smooth and glistening light pink membrane in which ran the blood vessels, which were congested and tortuous. An incision had been made through the testicle and showed a cut surface offering moderate resistance to the knife, light pink in color, homogenous, smooth and glistening. The general appearance was that of a new growth, rather firm in consistency, with edges that were rounded and slightly more hemorrhagic than the center. The epididymis and vas presented nothing abnormal. Another specimen measured 8 by 3 by 0.5 cm., and consisted of the vas deferens and spermatic artery with a large amount of adherent tissue. It presented nothing abnormal. A diagnosis of sarcoma of the testicle was made.

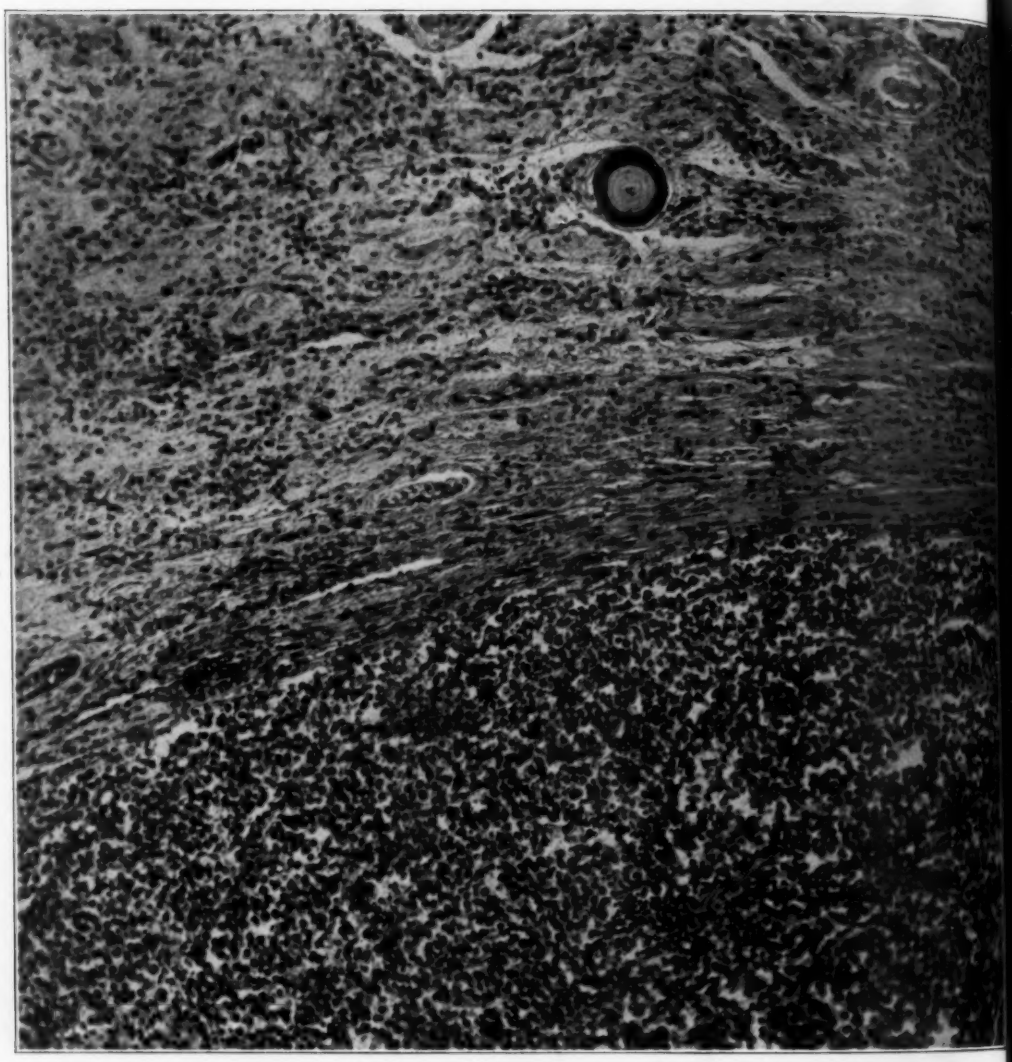

Fig. 10 (Case 6).—Photomicrograph of a section of the tumor. A diagnosis of teratoma of the testicle was made.

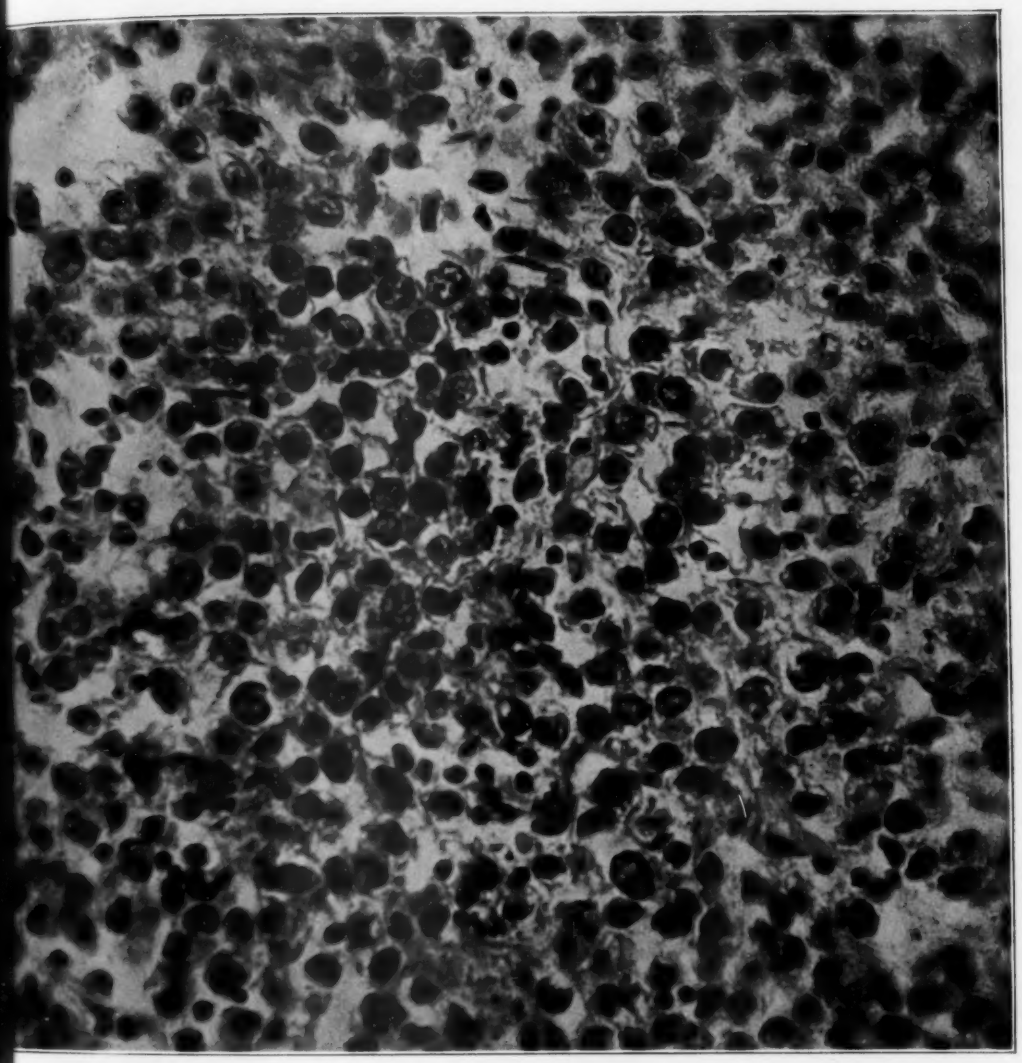

Fig. 11 (Case 6).—High power magnification of a section of the tumor. The diagnosis as made by Drs. John Lanford and James Ewing was teratoma of the testicle; by Dr. L. Clarence Cohn, embryonic carcinoma of the testicle.

A second study of the specimen was made and the following report submitted by Dr. Lanford: The sections from other areas of the testicle showed a slightly different picture from the first examination, and with the use of special stains the predominating cell was found to be epithelial, and, therefore, the condition was most probably made up of several types of structures such as one sees in teratomas of the testicle. The component cells were very embryonal showing many mitotic figures, and while some effort was made to arrange themselves in groups, the stroma was very scanty (figs. 10 and 11).

After the operation, I corresponded with Dr. William B. Coley with reference to any suggestions he would make regarding the after-care. He suggested radium packs and prophylactic treatment with toxins for several months.

On June 8, radium packs were applied over the left iliac region and the left lumbar region, for a total of 5,400 mg. hours. Erysipelas and prodigiosus toxins (Coley's) were given in increasing doses.

On July 16, the patient's general appearance was excellent. He consulted Dr. Matas in New Orleans and later went to see Dr. Coley in New York. In a personal communication, dated July 9, 1925, Dr. Coley stated that he found him in splendid physical condition.

The specimen was examined by Dr. Ewing for Dr. Coley, and his report coincided with that of Dr. Lanford, that the tumor was a teratoma.

A specimen was sent to Dr. Joseph Bloodgood, and during his absence, Dr. L. Clarence Cohn, his associate, reported the following: "In this case also, I would be more inclined to think we are dealing with an embryonic carcinoma of the testicle rather than a teratoma. In addition to the tumor, we saw normal testicle. The tumor was again of the very cellular large round cell type and there was no evidence of cartilage or myxoma."

At the present time, five years and three months since the operation, the patient is apparently in the best of health and presents no evidence of a recurrence.

Case 7.—Examination of the abdomen of Mr. A. R. did not reveal any masses, pain, tenderness or rigidity. Examination of the genitals revealed the right testicle to be swollen, tender and hard to the touch. It measured about 10 cm. in diameter; the skin was not adherent or red.

The following operation was done: Incision was made from about the middle of the scrotum upward over the inguinal canal. The aponeurosis of the external oblique was incised; the cord was separated from the surrounding tissues, ligated high, doubly transfixed, and the vas ligated independent of the vessel. Then the testicle was removed with the cord in toto.

The following laboratory report was made by Dr. Lanford: We received an oval mass of tissue which measured about 8.5 by 5 by 4 cm. The mass was fairly firm and nodular being composed of varying sized ovoid masses, loosely connected, ranging in size from that of a sparrow's egg to that of a small hen's egg. The outer surface of the mass was covered by a loose, rather rough appearing, pale pink membrane which slid loosely over the growth. Between the main mass and the irregular mass there appeared an open space which contained a small amount of straw-colored fluid. The irregular mass was found covered with a rather thick, fibrous, glistening white to pale pinkish-yellow coat through which a few tortuous blood vessels could be seen. In the region of the globus minor, there was a small deposit of fatty tissue and a spherical cyst about the size of a pea filled with straw-colored fluid. Section into the mass offered moderate resistance, and there appeared a moist, lobular surface for the most part pale pinkish cream in color and cellular. There were a few scattered, irregularly outlined, yellowish areas of necrosis and near the lower pole there was a rounded

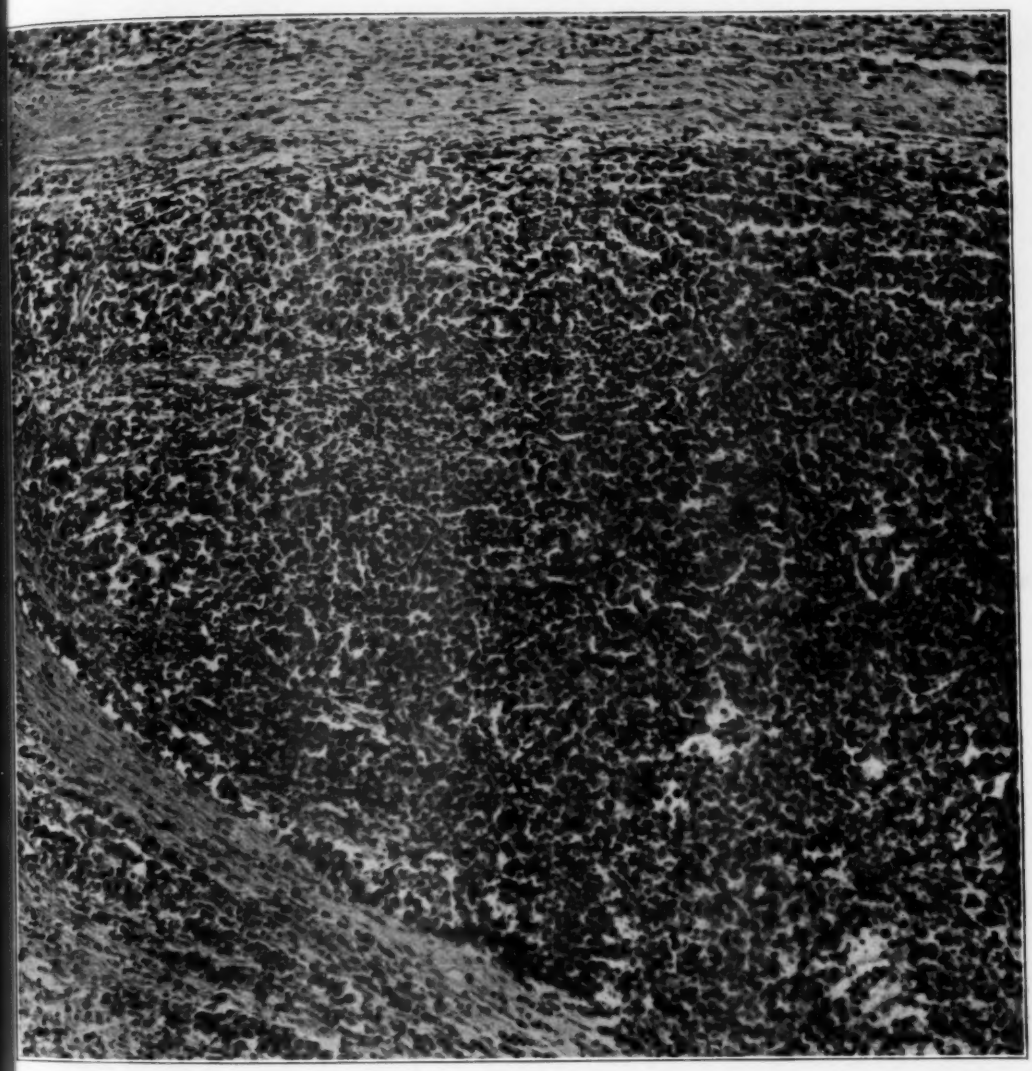

Fig. 12 (Case 7).—Photomicrograph of a section of the tumor. The diagnosis as made by Dr. John Lanford was teratoma of the testicle; by Dr. L. Clarence Cohn, embryonic carcinoma.

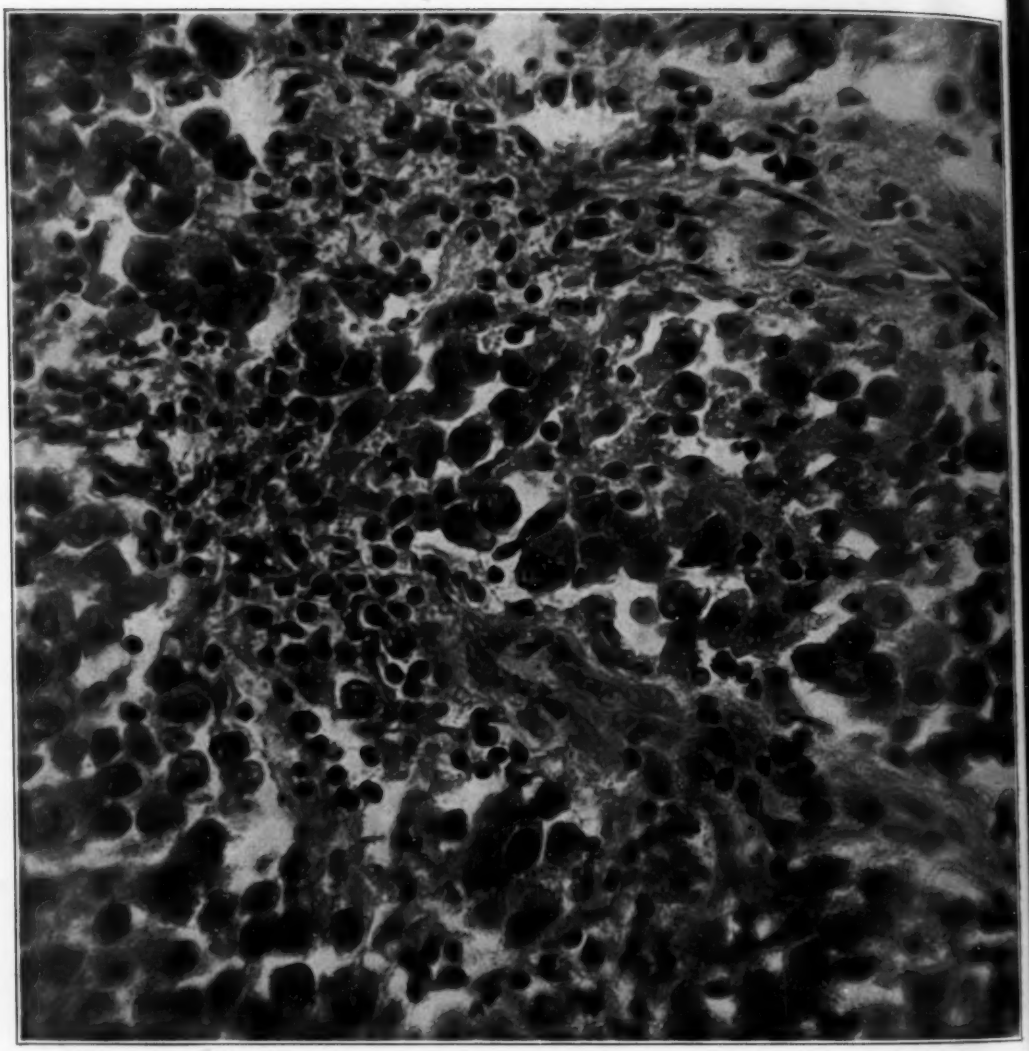

Fig. 13 (Case 7).—High power magnification of the tumor in case 7.

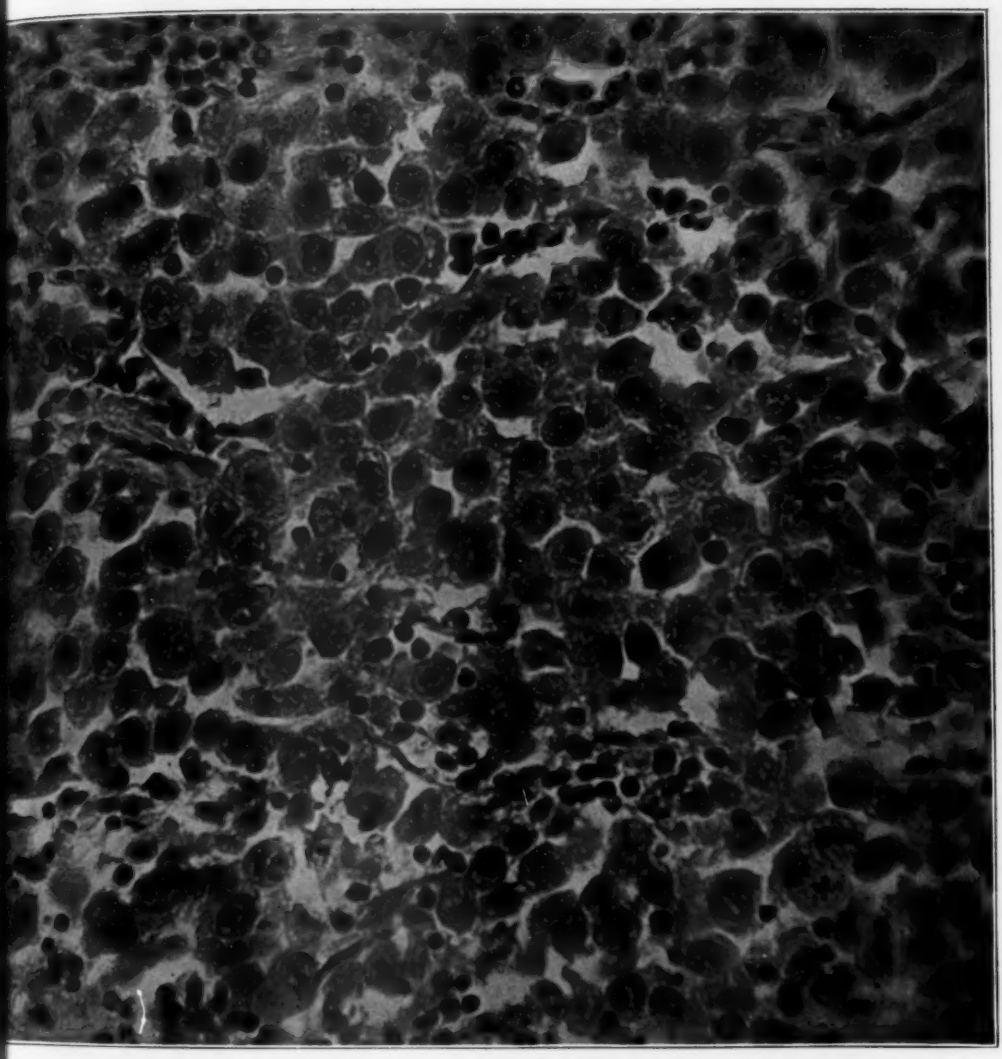

Fig. 14 (Case 7).—High power magnification of the tumor in case 7.

area about 2.5 cm. in diameter, gray to dark red and apparently even more cellular than the other region.

A diagnosis of teratoma was offered by Dr. Lanford. The sections showed many round embryonal cells making but little effort to differentiate, although there were suggestions of glandular structure (teratoma, figs. 12, 13 and 14).

During Dr. Bloodgood's absence, Dr. L. Clarence Cohn, his associate, reported: "Section shows a very cellular tumor in which the cells are arranged chiefly in large clumps and are of the large round cell type. I see no evidence of cartilage or myxoma or anything that would lead us to a diagnosis of teratoma. Therefore, we are placing this tumor under embryonic carcinoma of the testicle."

On June 7, 220 mg. of radium was applied on the right side of the abdomen and the right lumbar region for twenty-four hours.

On June 8, Coley's toxins, 1 minim in 5 minims of freshly distilled water, were given and daily increasing doses were to be given until a reaction was obtained, after which toxins were to be given every other day for three months.

The patient continued to receive toxins. When last seen he had no evidence of a recurrence. The social service reported that in July, 1930, he was working every day and feeling fine.

Comment.—These three cases are too few on which to base any conclusions. They are worthy of comment, however, because the treatment followed certain definite impressions gained through experience and evaluation of the literature.

In the first place, surgeons must not become enthusiastic for a radical operative procedure because of statistical results based on the experience of a few masters who have devoted many years to the perfection of their own technic. I wish to call attention to the enthusiasm of Lane for colectomy and for immediate operation for simple fracture; of Young's enthusiasm for perineal prostatectomy and of Finsterer's enthusiasm for gastrectomy in duodenal ulcers, and last, but not least, of the well known Wertheim operation for carcinoma of the uterus which may well be compared to the radical operation for teratoma as advocated by Chevassu and Hinman in this country.

Most of these procedures have not been accepted and some of them have been entirely discarded, not because of anything inherently wrong, but the magnitude of the procedure did not seem justified for general adoption. Dissatisfaction with routine procedures leads men to try new methods which, though they are associated with greater mortality, seem to result in higher percentages of cures.

The radical operation for teratoma seems logical because its object is to remove along with the involved elements the lymph glands which receive drainage from the diseased areas. I believe that this is essentially the reason that made Hinman advocate radical operation which includes removal of the retroperitoneal glands by the abdominal route in teratoma of the testicle. He has collected seventy cases in which radical operation has been done; ten were personal cases. The primary

operative mortality for the series according to Hinman was 12.6 per cent. Twenty-four patients died of metastases, and six more were known to be living at the time of the report with metastases. According to Hinman, the great majority of those who died of metastases died within one year. He further observed that in cases in which metastases is palpable the condition is inoperable; in addition to this, he says that in twenty-five cases in which radical operation was performed and in which there was no microscopic evidence of metastases in the glands, eight of the patients died later of "postoperative metastases."

One of his conclusions from this last observation should be carefully noted by any surgeon attempting the operation. "Postoperative metastases to the same lymph-bearing area clearly indicates that the original operation rather than being unnecessary, because of failure to find metastases, was insufficiently radical." Analysis of the foregoing statement is essential.

A primary mortality of 12.6 per cent is staggering to say the least; and that is not the mortality rate that the average surgeon would have. I fear that it would be more nearly 25 per cent if this procedure were attempted by the surgeon who removes an appendix or gallbladder with facility. It is also true that an attempt to remove the retroperitoneal glands high up on the aorta is likely to make an otherwise bold surgeon rather timid. Experience in radical operations on the breast where one is working in an easily accessible area proves the incompleteness of the removal of the entire lymph gland-bearing area. Further, if one succeeds in removing all of the apparent gland-bearing tissue, the eight cases cited by Hinman in which the patient died of postoperative metastases, indicate the difficulties incident to recognizing and removing all of the tissue necessary for the operation to be considered radical. Even then one cannot feel safe.

If embryology is to be considered, one should not forget that the abdominal lymph channels find their way above the diaphragm to the mediastinal glands and later by the receptaculum chyli to the lymph glands in the supraclavicular fossae and even into the blood stream. According to Dean, the left supraclavicular glands are involved in 14 per cent of the cases, and the mediastinal in 6 per cent.

By what token can one be sure that these mediastinal glands are not already involved even though there is no roentgen evidence nor palpable enlargement of the supraclavicular glands when operation is undertaken? "Hope springs eternal in the human breast."

Coley expressed the belief that the "number of cures is not sufficiently increased by radical operation or removal of retroperitoneal glands to warrant the very considerable risk of such an operation."

His observation was based on seventy-eight personal cases of malignant diseases of the testicle.

Because high ligation and castration followed by massive doses of radium and erysipelas and prodigiosus toxins (Coley's) offers some hope for cure without the appalling primary mortality of 12.6 per cent, and probably greater in my hands, I have been led to use the combination, and I must say that I am not sorry.

The patient who presented himself with a retroperitoneal metastases lived nearly two years with a known metastases, during which time, apparently as a result of treatment, he showed marked regressions in the size of the mass. At no time did he present edema or ascites. This is attributable to the location of the metastasis. The extent of the metastases to the mediastinal and supraclavicular glands indicate to my mind that in this case a so-called radical operation would not have prevented the dissemination beyond the diaphragm which would eventually have caused his death. The clinical syndrome that characterized this case included intense abdominal pain, digestive disturbances, emaciation, and the roentgen evidence of extrinsic obstructive phenomena.

The other two cases in which the patients have so far remained well, two and five years, respectively, are of interest because the treatment consisted of orchidectomy with high ligation followed by applications of radium (over the abdomen and lumbar region) and the persistent use of toxins. The plan of treatment needs no defense at my hands. I am taking this opportunity to add my word of confidence in the toxins. Coley's personal results are convincing.

In the beginning of the paper, it seemed to me that it would be necessary to apologize for presenting together a group of cases such as are here included.

Retroperitoneal tumors were discussed before the Southern Surgical Association in 1897 by Dr. Richard Douglas of Nashville. At that time he called attention to the fact that in 1889, Rogowski had collected twenty cases of solid retroperitoneal tumors. Each of these were histologically sarcoma.

Van der Veer, in 1892, discussed the subject of retroperitoneal tumors before the American Surgical Association.

The rarity of retroperitoneal tumor may be more apparent than real. One is aptly reminded by Hertzler, "Whenever one is confronted with a condition the diagnosis of which is exceedingly uncertain and its treatment is fraught with difficulty or disaster, it is more than probable that the number of cases that are reported bears a very uncertain relation to the number of cases that actually are observed." Few men take any great pleasure in reporting a case in which a diagnosis

was wrong and the treatment was a failure. When one has made a blunder and never finds out just what happened, this makes a poor text for a paper.

I found further reason for grouping these cases together for differential diagnostic purposes in some of the frank statements of men like Hertzler. He recorded one case in which a patient 23 years of age presented himself with a tumor extending from the costal margin to the false pelvis. The tumor was irregular in outline, firm and elastic. A diagnosis of hypernephroma had been made by another surgeon following an exploratory incision. Hertzler's own diagnosis was retroperitoneal sarcoma, but operation was not done by him.

At autopsy, he recorded finding a primary nodule in the left testicle, which proved that the tumor was probably a metastasis from teratoma of the testicle. In his case the confusion of metastasis from a teratoma with a hypernephroma is rather comforting, since in one of the cases presented here a retroperitoneal sarcoma was mistaken for a splenomegaly of unknown origin.

My primary object of trying to find diagnostic evidence has led to a review of the observations of previous contributors to this subject with reference to manifestations that were present in other cases.

Douglas stated:

> The patients exhibit a pronounced constitutional disturbance. The usual size of the tumor and its location give rise to disturbance of digestion and respiration. The kidneys are frequently displaced and the lymphatics of the digestive tract are partially obstructed consequently the patients are usually emaciated, not infrequently have nausea and vomiting and a pronounced cachexia is developed. The tumors are usually asymmetrical. Contrary to what one would suppose these tumors are sometimes decidedly influenced by respiration.

It was this last manifestation, described by Douglas as long ago as 1897, which influenced me to make the diagnosis of a splenic enlargement rather than a retroperitoneal mass in the case of J. P. The tumor mass in his case extended well below the umbilicus on the left side, was firm, nodular and moved with respiration. This movement with respiration seemed to be confirmed by fluoroscopic examination. No one has yet improved on Douglas' description.

A diagnostic manifestation of considerable importance is the relationship of the bowel to the tumor. Hertzler and others called attention to the fact that the "chief point in determining the retroperitoneal character of any tumor is the determination of its relation to the colon." The colon should be in front or displaced to the side by the tumor. This relationship should be determined by roentgen evidence shown by an opaque meal.

It is generally conceded that retroperitoneal tumors present less mobility than intraperitoneal tumors, though both intraperitoneal and retroperitoneal tumors present roentgen evidence that suggests extrinsic obstruction of the bowel rather than intrinsic manifestations. The more one studies such cases the greater the difficulty in accurate differential diagnosis seems to be.

Just a word in connection with the surgical treatment for these cases. A paragraph taken from Douglas' paper written in 1897 very well summarizes what might be taken to be the present status:

> According to Mr. Cripps, they (retroperitoneal sarcoma) do not recur when removed. I think the speaker was very safe in making this assertion, inasmuch as about 95% of the patients die from the operation or before it.

SUMMARY AND CONCLUSIONS

1. This report includes retroperitoneal masses which were apparently primary new growths; some that were metastatic new growths and others corresponded in pathologic signs to the clinical picture which is labeled Hodgkin's disease.

2. Retroperitoneal masses may be present and yet remain undetectable during life by any available diagnostic methods.

3. The roentgen evidence of extrinsic obstructive intestinal phenomena is interesting and diagnostic when present, but the absence of such a sign is by no means acceptable as evidence that a retroperitoneal growth does not exist.

4. Retroperitoneal tumors sometimes move with respiration, thus making it difficult, if the mass is on the left side, to eliminate splenomegalia.

5. The symptoms caused by a retroperitoneal growth are dependent on the location of the growth. Proximity to the celiac plexus causes digestive phenomena, whereas growths even of larger size in other locations may not cause digestive disturbances. Digestive disturbances are not diagnostic as they are present in so many conditions other than retroperitoneal tumors.

6. Anemia is present in many cases of retroperitoneal growths, but is not to be relied on as a diagnostic phenomena.

7. Anemia and digestive disturbances may mislead one to treat the patient for an entirely different condition.

8. Edema of the extremities and ascites are present when the growth is large and when it is so situated as to interfere with the venous return. A growth situated on the right side readily produces edema, whereas a large growth on the left side may not be associated with edema of the lower extremities or ascites.

9. Retroperitoneal masses may be associated with chylous ascites and chylous pleural effusions.

10. Retroperitoneal sarcomas may be primary and productive of metastases. Other retroperitoneal sarcomas may be secondary growths.

11. Some retroperitoneal masses present the clinical picture of an infection, and the autopsy reveals for the first time that the patient had Hodgkin's disease.

12. At present it seems justifiable to conclude that Hodgkin's disease is an infection.

13. When searching for the primary cause of retroperitoneal metastases, teratoma of the testicle must not be overlooked as a possible source.

14. The differential histologic diagnosis is apparently very difficult.

15. So far, my search for a group of manifestations which might help to clear up the puzzling clinical problem produced by retroperitoneal masses has failed to add anything of value.

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LIPOGRANULOMATOSIS (MAKAI) *

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BROOKLYN

Lipogranulomatosis is a rather common disease which is frequently overlooked and misinterpreted. A description of the individual lesions, the whole chain of which constitutes the entity of the disease described by Makai,[1] is repeatedly met with in the literature of the last twenty years. According to Makai, the lesion is due to necrosis of the subcutaneous fat tissue, transformation of its neutral fats into fatty acids or soaps and inflammatory reaction of the surrounding tissue. The result is a granulation tissue, frequently of epithelioid cell character, suggestive of tuberculosis. This similarity is further stressed by the large number of giant cells, some of which are of the ordinary foreign body type, while others are of the characteristic Langhans type. The granulation tissue is finally substituted by fibrous scar tissue in which inclusions of necrotic and even calcified material are met with; or the scar tissue encloses cystlike cavities, the result of liquefaction.

My associates and I observed three cases of lipogranulomatosis at the Crown Heights Hospital on Dr. H. Koster's service. We were also able to demonstrate these cases to Dr. Makai, who happened to be on a visit to this country. A brief description of the three cases follows:

REPORT OF CASES

CASE 1.—Irene D., aged 20, was admitted to the hospital because of several small nodules on the right arm and left thigh. She had noticed their development some years previously, after she had received a number of subcutaneous injections while suffering from pneumonia. There was a hard nodule, the size of a bean, in the region of the deltoid muscle of the right arm. The nodule was slightly raised above the surface, and the skin did not fold over it. There was another nodule about the size of a hazelnut on the external surface of the left thigh. The latter was not as sharply demarcated from the surrounding fat tissue as the nodule on the arm. Neither nodule was tender. On Sept. 23, 1930, the nodules and the overlying skin were removed. Healing occurred per primam intentionem, but was prolonged for fourteen days. After operation, subcutaneous injections of morphine were made into the right thigh, and a painful area of infiltration, the size of a nickel developed, which lasted a week and then disappeared.

Histologic examination of the specimen showed a small round nodule, 5 mm. in diameter, embedded in the fat tissue. It was surrounded by a fibrous capsule composed of dense hyaline fibrils circularly arranged. Inside of this layer, there was a stratum of granulation tissue which was interwoven with heavy strands

* Submitted for publication, Jan. 8, 1931.

* From the Department of Pathology, Crown Heights Hospital.

1. Makai, E.: Klin. Wchnschr. **7**:2343, 1928.

of hyaline fibrils. The cells of the granulation tissue were lymphocytes, fibroblasts and larger cells with pale nuclei of the endothelial or macrophage class. The main central part of the nodule was honeycombed. Some of the vacuoles of this area were large and irregular; others were smaller, approximately the size of ordinary or overgrown fat cells. All of the vacuoles were separated by strands of hyaline fibrils and occasional areas of granulation tissue. The latter showed an abundance of large macrophages and cells with foamy cytoplasm suggesting young fat cells. The wall of the cysts and smaller vacuoles was lined by a syncytial seam, with scattered rod or spindle shaped, darkly stained nuclei. Occasionally, these nuclei were grouped eccentrically to present a crescent-shaped

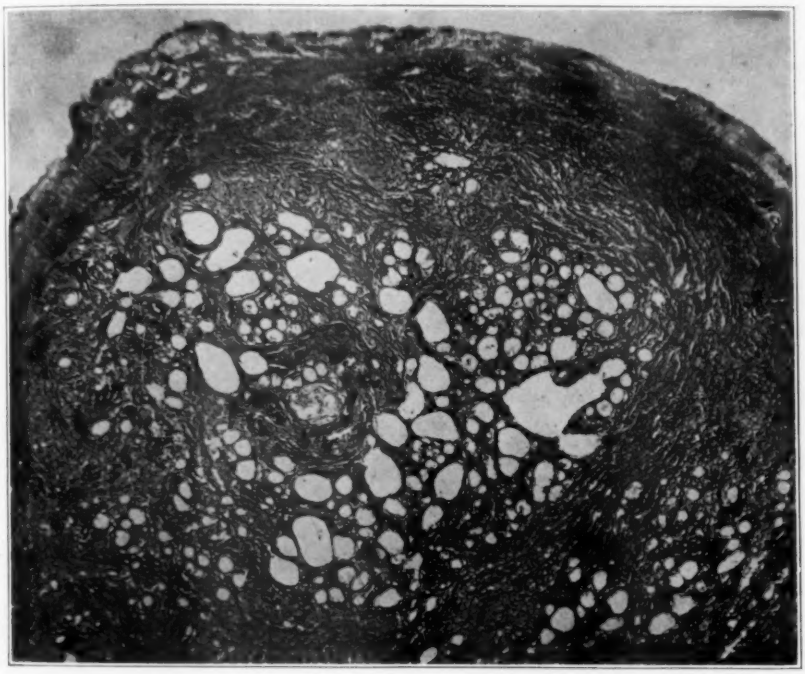

Fig. 1.—Low power view of a nodular lipogranuloma. A fibrous capsule, honeycombed structure and calcification are seen about the necrotic center.

giant cell. Some of the vacuoles contained regular foreign body giant cells, the cytoplasm of which projected irregularly into the lumen. In some of these vacuoles, there was amorphous material which stained a diffuse purplish blue with hematoxylin. The center of the nodule was occupied by another, more densely fibrosed area, the periphery of which showed plentiful amorphous, dark blue-stained deposits. This substance was apparently lime; it surrounded like a ring some poorly staining necrotic tissue. The nuclei in this area were not stained, and only the outlines of the tissue revealed that the area was of a character identical with that of the surrounding honeycombed structures.

Case 2.—J. B., a man, aged 49, was admitted to the hospital on Sept. 19, 1930, with a history of having been operated on about five years previously for bilateral inguinal hernia. He had noticed the recurrence of a mass shortly after he left

the hospital. At the time of admission, in the right groin there was a large palpable mass which extended into the scrotum. The patient was operated on (Galli operation) and made an uneventful recovery. About a week after his discharge from the hospital, he noticed a small swelling in the upper end of the incision. Wet dressings were applied, and the condition cleared up. One week later, the patient's physician noticed a hard, tender mass under the site of the incision. The patient did not have a rise in temperature, and the mass disappeared after the application of hot wet dressings. This mass recurred and disappeared several times at intervals of four or five days. On November 28, the patient was readmitted to the hospital. At this time the mass was very large, hard

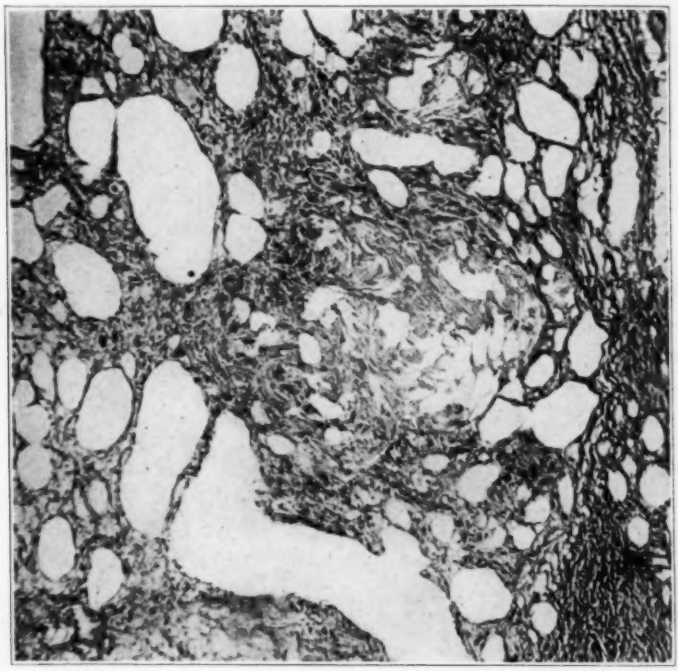

Fig. 2.—Low power view of necrosis of the fat tissue, surrounded by granulation tissue.

and tender, and there were small pinpoint openings along the scar from which clear lymph could be expressed.

The old scar was excised, and dense fibrous tissue was found subcutaneously above the deep fascia. The entire granulomatous mass was excised and the wound closed. The patient made an uneventful recovery. Histologic examination of the specimen showed that the fat tissue was interspersed with areas of hyaline scar tissue. Enclosed therein were numerous foci of groups of lymphocytic cells or small areas of cellular granulation tissue. Single giant cells or small groups of giant cells were also seen, directly surrounded by scar tissue or separated from the latter merely by a wreath of lymphocytes. Several islands of the fat tissue within the scarry area presented a multitude of young, fat cells with foamy cytoplasm in mosaic arrangement. They formed septums between the vacuoles of

the old fat tissue. In other places, there was evidence of intracellular regeneration of the fat tissue. In the center of this area, where the young fat cells were densest and their cytoplasm stained most intensely owing to the lack of lipoid content, there was a small focus of necrosis with needle-shaped rents between the poorly staining necrotic material. Other places of the scar tissue revealed the presence of quite large, oval, single cavities. There was a scanty syncytial seam on the inside of these cysts, with a few scattered pyknotic nuclei. The cysts were enclosed by fibrous connective tissue, and there were no lymph or blood capillaries in their vicinity. They contained a more or less amorphous material, which proved to consist of fatty acids or a mixture of fatty acids with cholesterol esters, as was shown by the results of Benda's or Fischler's stain.

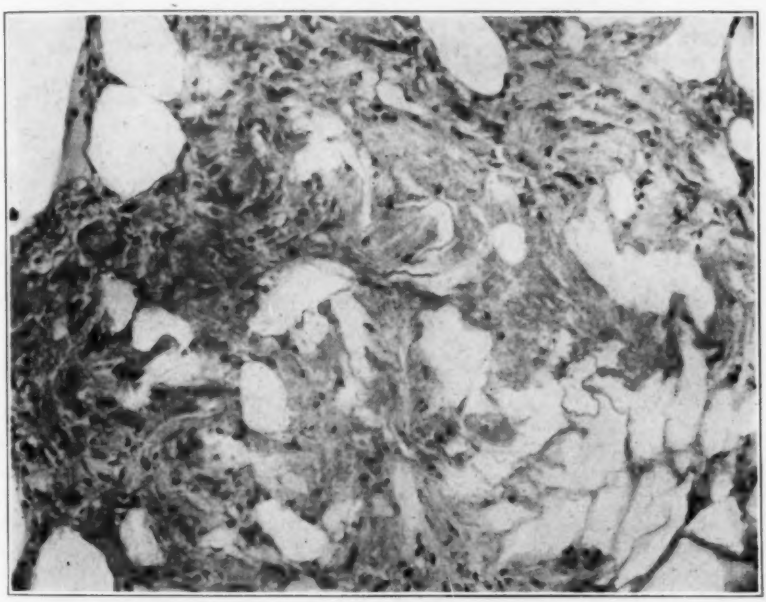

Fig. 3.—Detail of figure 2, showing a necrotic area and adjacent giant cells.

Case 3.—Rebecca B., aged 37, was admitted to the Crown Heights Hospital with an irregular mass the size of a hen's egg in the medial portion of the right breast. She had noticed the growth of the nodule for the last few months. She could not recall any trauma or any other reason for the growth.

The mass was of an even surface, easily movable and not adherent to the skin. The tumor was excised on Nov. 19, 1930. During the operation, several small cavities opened up which contained a brownish viscous fluid. The diagnosis of galactocele was made. Healing took place per primam intentionem, but, after two weeks the wound reopened spontaneously, and a hematoma the size of a walnut was found in the fat tissue. An histologic examination was made of the specimen. The glands of the breast showed irregular fibrosis, cystic changes of the glandular parenchyma and cystic dilatation of the lactiferous ducts. The stroma of the glands of the breast and the fat tissue between the lobules of the gland showed an accumulation of round cells, particularly about the blood vessels. There was a small nodule encapsulated by hyaline connective tissue, which consisted mostly

of large epithelioid cells, the projections of which formed a fine reticulum. Between these cells, but particularly surrounding the nodules of epithelioid cells, there was a massive aggregation of lymphocytes. In the center of these nodules there were irregular open spaces which were lined by syncytium, the latter forming giant cell-like structures. In other places, the irregular vacuoles were surrounded by one or several real giant cells from which filament-like projections extended toward the center. On frozen section, crystalline lipoid material, probably cholesterol crystals, was demonstrated, surrounded by the pseudopods of the giant cells. In the vicinity of the area described, but directly within the hyaline scar tissue, several giant cells were found each surrounded by a few

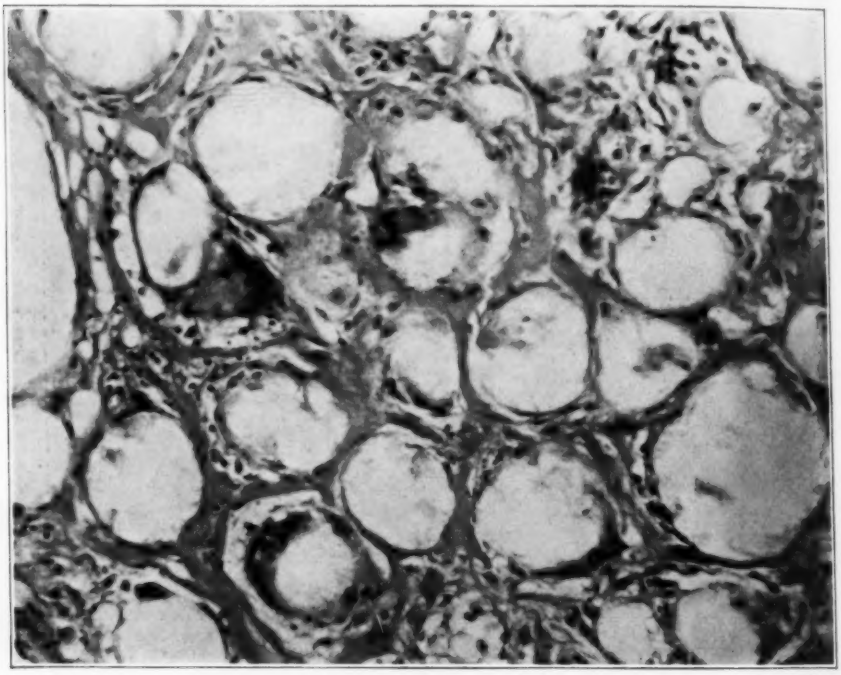

Fig. 4.—Giant cells forming about fatty acid and cholesterol crystals.

lymphocytes. The cytoplasm of these giant cells showed vacuoles divided up by fine protoplasmic filaments and containing fatty material, as shown on frozen section.

COMMENT

In summarizing the observations in these three cases, it can be said: 1. There is a chronic, inflammatory, productive process resulting in the formation of fibrous scar tissue. This tissue develops from granulation tissue which in places is quite cellular and not different from ordinary granulation tissue; in other places, epitheloid cells predominate and form groups resembling tubercles of epitheloid cells. The presence of large giant cells of foreign body type adds to the apparent similarity.

2. Necroses are present, sometimes with the outlines of the decaying tissue fairly well preserved and sometimes transformed into amorphous débris. Diffuse bluish coloration in slides stained with hematoxylin suggests the presence of calcium soaps, as seen in pancreatic fat necrosis. Needle-shaped rents indicate the former presence of cholesterol crystals which can actually be demonstrated in frozen sections. Massive deposits of lime in and about the necrotic foci were present in two of the cases.

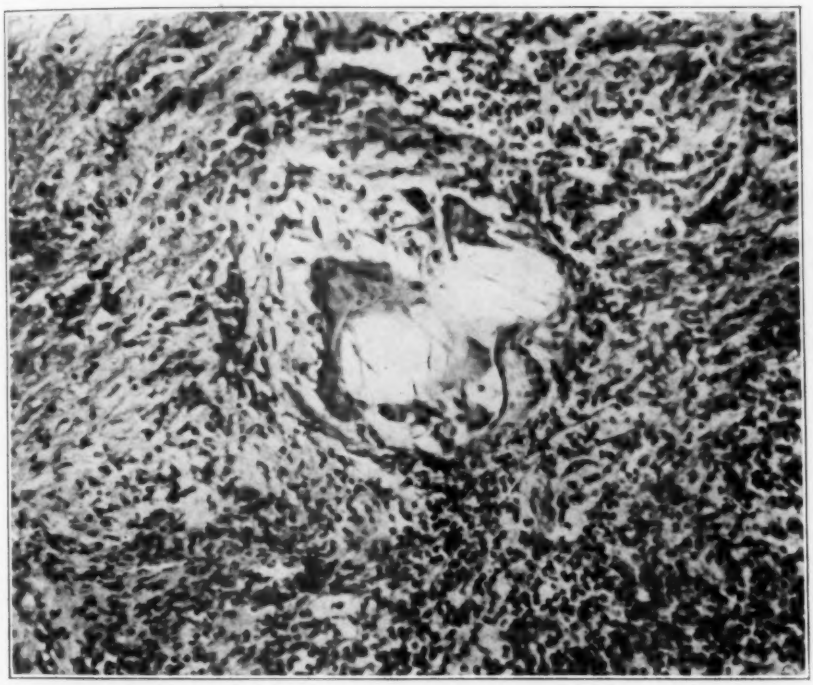

Fig. 5.—Large, single giant cell surrounded by granulation tissue.

3. The changes in the fat tissue can be divided into two groups. On the one hand, there is a new formation of small fat cells. Their lipoid content does not dissolve in the paraffin sections. Their cytoplasm is finely granular and moderately basophilic. These young fat cells seem to form between the old fat cells, but their endogenous development within the body of the old cell is actually demonstrable in many instances. The remaining fat droplet then appears, surrounded by cells which are sometimes multinuclear. The other type of change consists in the appearance of large vacuoles, from two to three times as large as an ordinary fat cell, but sometimes exceeding these dimensions many times. Some of these fat cysts are large enough to become visible to

the naked eye. These cysts are lined with a syncytial protoplasmic seam in which scattered nuclei may be seen, or the nuclei group together eccentrically and appear in the form of a crescent-shaped giant cell. Fat cysts occur singly or in groups which are separated by hyalinized connective tissue fibrils. They usually contain fatty material, particularly fatty acids, more or less diluted with serous fluid.

The changes observed in these three cases do not cover the whole scale that previous observers have attributed to the cycle of lipogranuloma. Abrikossoff [2] classified the changes in five groups. The first

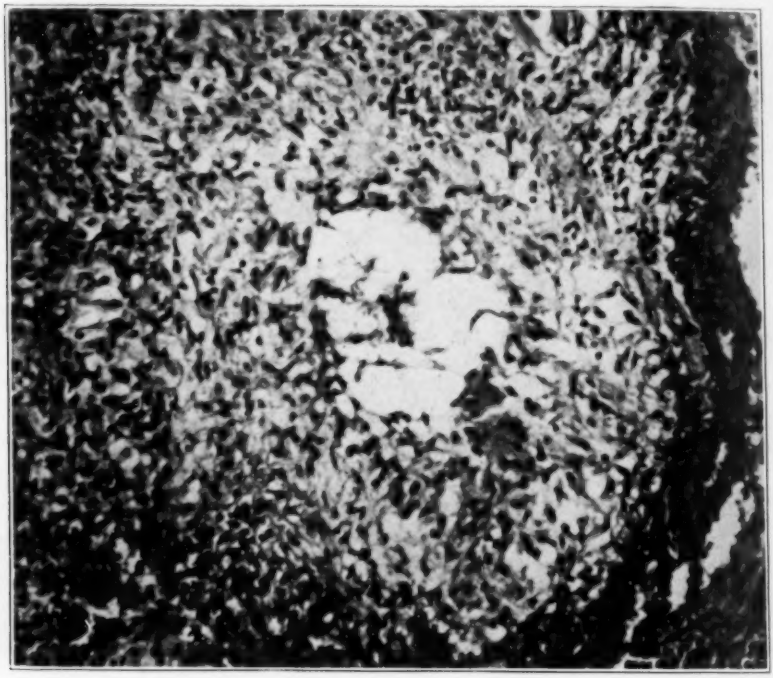

Fig. 6.—Epithelioid cell nodule with central vacuole.

includes the early forms of epithelioid cell granulations with subsequent progressive fibrosis. The second is represented by the appearance of cysts, some of which may fill up with serous fluid after absorption of their fatty content. The third appears as a completely fibrotic nodule characterized by many small foci built by concentric arrangement of their hyaline fibrils. The fourth stage is closely related to the previous one and differs in the presence of calcareous deposits in the center of the concentric hyaline structures. The fifth group presents the picture of complete petrifaction and corresponds to that which is known as a fat tissue stone.

2. Abrikossoff, A.: Verhandl. d. deutsch. path. Gesellsch. **24**:57, 1929.

The various authors mostly agree as to the histogenesis of lipogranuloma. The consensus is that the changes set in with necrosis of the fat tissue followed by the formation of granulation tissue, progressive scarring and finally calcification. The formation of giant cells and of cysts, particularly the larger ones with serous content, however, has given rise to diverging interpretation. Makai expressed the belief that the giant cells are at least partly the products of proliferating capillary endothelium, and observation of serous cysts has led several Russian authors (Schujeninoff [3] and Kedrovsky [3]) to classify these lesions as

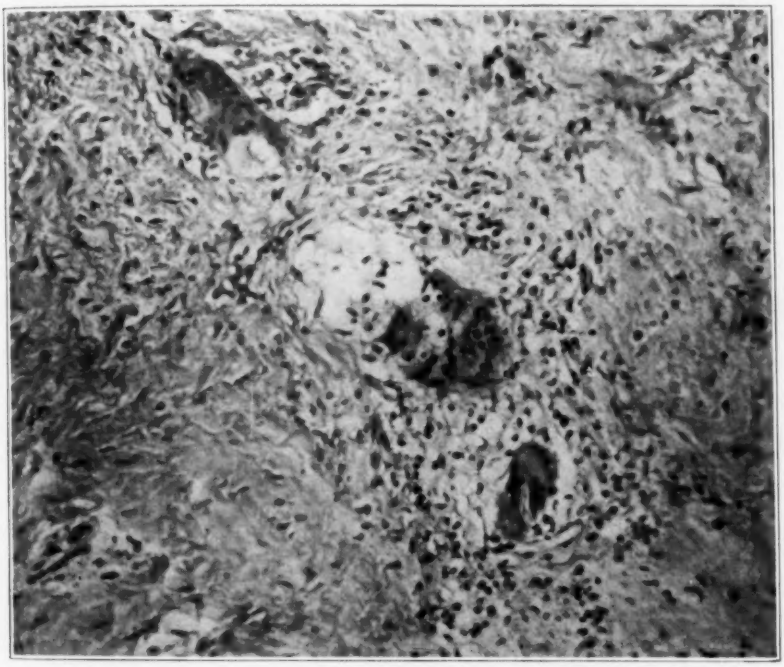

Fig. 7.—Giant cells in the scar tissue.

"cystic lymphangitis." Abrikossoff pointed out that there is no need for this assumption. The formation of giant cells of this type is closely linked with two processes: the regeneration of fat cells and the response of macrophages to the presence of free extracellular fatty material. Special stains (Sudan, Benda's and Fischler's stain) reveal the presence of fatty material in the cytoplasm of the giant cells and identify them as genuine "foreign body" giant cells in contradistinction to giant cells such as occasionally form through hasty and incomplete division of proliferating endothelium. Abrikossoff drew attention to the simi-

3. Quoted by Abrikossoff (footnote 2).

larly erroneous interpretation of changes commonly observed in dermoid cysts, in cases in which their walls had been invaded by some of the fatty material. The giant cells that develop in such places have been derived from the endothelium of lymph vessels (Stuebler,[4] Schottlaender [5] and Gentili [6]), but it seems more logical to ascribe their origin to proliferation of ordinary macrophages.

Etiologic factors in the pathogenesis of lipogranulomatosis are manifold. Whether the cause is trauma, inflammation or a circulatory dis-

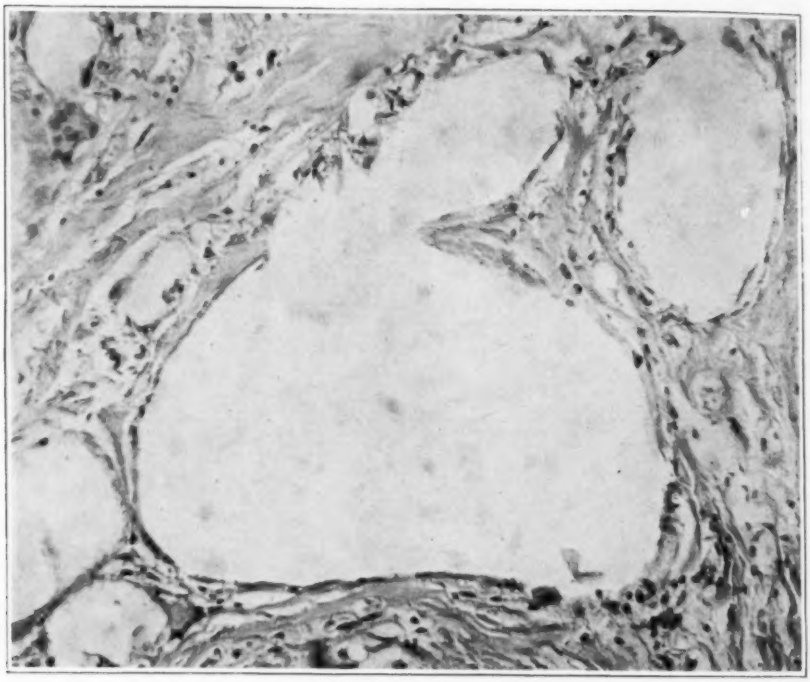

Fig. 8.—Large fat cyst with syncytial lining.

turbance, they all act in the same way—they injure or destroy the fat cells. According to Makai, the injured fat tissue is susceptible to the effect of the lipase, the existence of which in the subcutaneous fat tissue has been demonstrated by experimental work. When liberated from injured fat tissue, this lipase leads to the decomposition of the fat whereby fatty acids and other lipoid materials are liberated. These

4. Stuebler: Virchows Arch. f. path. Anat. **247**:159, 1923.
5. Schottlaender: Arch. f. Gynäk. **78**:137, 1906.
6. Gentili: Arch. f. Gynäk. **77**:616, 1905.

substances act as foreign bodies and stimulate the formation of giant cells (Berner,[7] Heyde,[8] Farr,[9] Knape,[10] von Gierke[11] and Askanazy.[12]

The close resemblance of the necrotic foci in the fat tissue to fat necrosis of the pancreas has suggested the possibility that pancreatic lipase may be the acting enzyme. However, von Gierke's experiments have shown that such changes also occur in vitro without the possibility of pancreatic interference.

In view of the frequency with which impairment of the subcutaneous fat tissue ought to and does occur, it seems peculiar that lipogranulomatosis is not more common. Since attention has been called to the existence of these lesions, they have been found more frequently than in the past, yet their frequency remains much below that of causes likely to elicit these changes. This consideration induced Makai to suggest a constitutional factor that may possibly depend on endocrine influences. Similar views were also suggested by Brancati. It has been reported that the administration of thyroid has a beneficial effect on such lesions (Bessau[13]), and in one of Makai's cases cod liver oil also gave favorable therapeutic results. At present the endocrine concept seems so hypothetic that its discussion is hardly warranted before the accumulation of further facts. However, it seems of importance, as Makai emphasized, that the healing of wounds in these patients is often prolonged and yields massive, ugly scars in spite of primary union. This observation strengthens suspicion that some constitutional factor is at play. The frequent multiplicity of the lesion and its tendency to recur, as observed in case 2, also point in the same direction.

In reviewing the literature, a number of references are available to show that lipogranulomatosis may occur in any part of the body that harbors fat tissue. From the surgeon's point of view, perhaps the greatest importance might be attached to the lipogranuloma that arises in the glands of the breast. Such observations were recorded by Targett,[14] Lanz[15] and Berner,[7] but their clinical significance was not properly stressed before the publication of the paper of Lee and Adair,[16] and particularly that of Hadfield.[17] The latter author collected forty-two cases on record under the heading of "fat necrosis of the breast."

7. Berner: Virchows Arch. f. path. Anat. **187**:360, 1907; **193**:510, 1908.
8. Heyde: Deutsche Ztschr. f. Chir. **109**:500, 1911.
9. Farr, R. E.: Ann. Surg. **80**:670, 1924.
10. Knape: Virchows Arch. f. path. Anat. **207**:321, 1912.
11. von Gierke: Verhandl. d. deutsch. path. Gesellsch. **15**:433, 1912.
12. Askanazy, M., and Jentzer, A.: Wien. med. Wchnschr. **79**:3, 1929.
13. Bessau, G.: Monatschr. f. Kinderh. **38**:438, 1928.
14. Targett: Tr. Path. Soc., London **47**:249, 1896.
15. Lanz: Zentralbl. f. Chir. **25**:1253, 1898.
16. Lee, B. J., and Adair, F. E.: Ann. Surg. **80**:670, 1924.
17. Hadfield, G.: Brit. J. Surg. **17**:673, 1930.

Other recent contributions on this subject are the papers of Gohrbandt,[18] Trnica,[19] Wellbrock[20] and Brancati.[21] Most of these authors emphasized the clinical resemblance of these lesions to early carcinoma. The differential diagnosis is often established only by histologic examination. It is far easier, however, to confuse the lesion of the breast with tuberculosis, and I feel inclined to believe that more than incidental diagnostic mistakes of this kind have been committed.

The most common seat of the lesion is the subcutaneous fat tissue, and the majority of the cases on record show this localization (Heyde,[8] Kuettner,[22] Moir,[23] Schujeminoff,[3] Kedrovsky,[3] Schamow,[24] Abrikossoff,[2] Makai,[1] Alexander,[25] Strasser[26] and others). In some cases the direct relationship to trauma was well established, as in case 1; in others, the perivascular infiltration of the subcutaneous tissue in typhus (Schujeninoff[3]) or the vocational injuries of the skin in working men (Kogan Jasny[27]) could be blamed. Their apparently frequent occurrence in amputational stumps has been noticed only recently (zur Verth,[28] Makai[29] and Protopow[30]) and seems to deserve the attention of the surgeon.

Lipomas are another comparatively frequent seat of lipogranuloma, as was known to Virchow. Targett,[14] Shattock,[31] Knape,[10] von Gierke[11] and others describe lipomas with secondary lipogranulomatous changes, usually of the calcifying type. Calcification, however, may also develop in single or multiple subcutaneous lesions (Chiari,[32] Huebschmann,[33] Lanz[15] and others) or may be widely scattered, as in Schamow's[24] remarkable case of "interstitial calcinosis."

Lipogranuloma occasionally develops in other parts of the body, such as the mesentery, retroperitoneal fat tissue and bone marrow. The immediate cause is always injury to the fat tissue, such as is produced by an invading tumor. A considerable number of observations have

18. Gohrbandt, P.: Arch. f. klin. Chir. **148**:684, 1927.
19. Trnica: J. Coll. Surgeons, Australasia **2**:21, 1929.
20. Wellbrock, W. L. A.: Ann. Surg. **90**:154, 1929.
21. Brancati, R.: Arch. ital. di chir. **26**:585, 1930.
22. Kuettner: Berl. klin. Wchnschr. **1**:9, 1913.
23. Moir, P. J.: Brit. M. J. **1**:64, 1929.
24. Schamow: Zentralbl. f. Chir. **51**:2221, 1924.
25. Alexander, A.: Klin. Wchnschr. **8**:2138, 1929.
26. Strasser, U.: Klin. Wchnschr. **9**:987, 1930.
27. Kogan Jasny: Ztl. Org. Chir. **39**:265, 1927.
28. zur Verth, M.: Arch. f. klin. Chir. **157**:55, 1929.
29. Makai, E.: Zentralbl. f. Chir. **57**:590, 1930.
30. Protopow: Zentralbl. f. Chir. **57**:206, 1930.
31. Shattock: Tr. Path. Soc., London **47**:246, 1896.
32. Chiari: Ztschr. f. Heilk. 1908, Suppl. quoted from v. Gierke.
33. Huebschmann: München. med. Wchnschr. **72**:1579, 1925.

recently appeared which call attention to the appearance of "granulation tissue with foreign body giant cells," i. e., lipogranuloma in fat tissue invaded by malignant growth (Fleischmann,[34] Gohrbandt,[18] Petri,[35] Teutschlaender,[36] Wellbrock[20] and others).

Pediatricians particularly have been puzzled by the peculiar changes of the subcutaneous fat tissue in scleroderma of the new-born (Bernheim-Karrer[37]) or subcutaneous fat necrosis with or without calcification (Farr,[9] Bessau,[13] Pozzo and Bianchi,[38] Heubschmann[33] and others). A more complete survey of the literature dealing with this particular phase of the subject can be gathered from the paper of Epstein and Barash,[39] who have discussed the question from the point of view of the pediatrician.

Finally, the dermatologists have paid considerable attention to lesions of a similar nature (Schwarzmann,[40] Lecène and Moulonguet,[41] Alexander[25] and others); yet, as pointed out by Makai and Abrikossoff, it seems that increasing knowledge of lipogranulomatosis may change some of the concepts concerning certain conditions of the skin, such as Darier's sarcoid, Bazin's indurating erythema and the various types of lesions summarized as tuberculids. It seems probable that toxic lesions or allergic reactions of the subcutaneous fat tissue account for the injury of fat cells which is followed by the development of the nonspecific lipogranuloma. When one looks at these lesions as reactions specific to fat tissue but nonspecific as far as the eliciting cause is concerned, one may attain a more satisfactory interpretation of tuberculids and allied changes.

It stands to reason that any disease that occurs in so many places of the body and in connection with such varied conditions is likely to be more or less misunderstood, particularly if its morphologic aspects also show variations over a wide range. It therefore seems of definite value to establish a common basis for these varied conditions expressed by a unification of nomenclature. The various names proposed in the literature, such as fat necrosis of the breast, fat stone, oleogranuloma, calcinosis interstitialis, cystic lymphangitis, chalazion (Schall[42]) and the various dermatologic terms each express but one phase in the devel-

34. Fleischmann, R.: Arch. f. klin. Chir. **158**:692, 1930.
35. Petri: Zentralbl. f. Path. **37**:1, 1926.
36. Teutschlaender, O.: Frankfurt. Ztschr. f. Path. **35**:436, 1927.
37. Bernheim-Karrer: Ztschr. f. Kinderh. **42**:658, 1926.
38. Pozzo, F., and Bianchi, A. E.: Arch. de méd. d. enf. **30**:529, 1927.
39. Epstein, J., and Barash, L.: Subcutaneous Fat Necrosis, Am. J. Dis. Child. **40**:337 (Aug.) 1930.
40. Schwarzmann, J. M.: Ann. de dermat. et syph. **1**:476, 1930.
41. Lecène, P., and Moulonguet, P.: Ann. d'anat. path. **2**:193, 1925.
42. Schall, E.: Arch. f. Ophth. **117**:662, 1926.

opment of the lesion or some peculiarity due to its localization. Makai deserves the credit for having opened the field for unified consideration of these varied but pathogenically identical changes. The name lipogranuloma expresses properly the histogenesis and character of the lesion. Its frequent occurrence in multiple, sometimes symmetric, foci (Strasser [26]) justifies the term lipogranulomatosis, which also includes reference to the possible constitutional factors.

SUMMARY

Three cases of lipogranulomatosis are described, two in the subcutaneous fat tissue and one in the breast. The histogenesis of the lesion is discussed, and its frequency and clinical importance are emphasized.

THE NATURE OF LIVING CELLS

WITH SPECIAL REFERENCE TO THE NATURE OF CANCER CELLS AND OF FATTY DEGENERATION *

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The research a preliminary report of which is here presented was undertaken with the purpose of discovering some physical principle that might account for the conversion of normal cells into cancer cells, that is, into cells the energy of which is used only for growth, whereas the energy of the tissue in which the conversion takes place is used primarily for function. It is clear that the cancer cell must owe its formation to the operation of existing laws of growth in the host. These laws are most strikingly illustrated in the process of fertilization.

The ovum and the sperm, as Keller has shown, exhibit opposite signs of charge, hence they attract each other. The preponderantly positive element exists apart from the preponderantly negative element, but when they unite growth and division take place, forming the beginning of a new organism. The fertilized ovum contains, therefore, elements bearing opposite signs of charge and electrolytes in optimum proportions, and transmits these characteristics to each cell of the developing organism.

Every living cell contains proteins, lipoids and electrolytes. Colloidal systems of proteins and of lipoids bear different degrees of electrical charge. We postulated, therefore, that if we were to mix proteins and lipoids with the electrolytes present in living tissues, the same laws would act that govern the process of fertilization; that is, that the comparatively positive element would combine with the comparatively negative element, this combination with the electrolytes carrying an electric charge and forming an organized unit which would present a cell-like form. In other words, we proposed to test by experiment whether or not after the essential fractions of the cells of an animal had been separated they could be reassembled to form a lower undifferentiated type of cell that would bear a certain physical resemblance to the cell from which the material of which it was made was derived, and would also exhibit some of the phenomena of the parent cells.

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* Submitted for publication, Jan. 27, 1931.

* From the Cleveland Clinic Foundation.

This research is by no means the first attempt to produce artificial cells. Such cells have been formed from inorganic and organic material by many investigators, notably Beutner, Butschli, Herrera, Le Duc, Lehmann, Loeb and MacDougal. The cells formed by these investigators have shown such phenomena as division, nucleation, growth and ameboid movement, but in cells made by their formulas, respiration, repeated division and prolonged exhibition of the manifested phenomena have not been observed. The cells of MacDougal showed a difference in ion concentration analogous to biologic cells. The investigations of Bastian and others are of a different type.

As we have stated, it has been our hope that from the study of undifferentiated cells made up of proteins, lipoids and electrolytes extracted from tissues, we might ultimately gain some insight into the processes whereby malignant cells are formed from the proteins, lipoids and electrolytes of their parent tissues.

To these cells thus formed from proteins, lipoids and electrolytes we have applied the term autosynthetic cells. We expected that, because of the potential differences between the elements from which they were synthesized, these autosynthetic cells would themselves carry an electric charge and would show growth energy; that they would divide, would have respiration and would show motility. The extent to which our expectations have been realized is stated in the following summary of experiments.

EXPERIMENTAL OBSERVATIONS

From the organs of freshly killed normal animals, the lipoids and proteins of the brain were extracted and the ash was obtained. By mixing the lipoids and the proteins of the brain and a solution of the brain ash or of the electrolytes contained in the brain, the process of fertilization in nature by the uniting of the spermatozoon and the ovum was imitated.

On observation of this mixture of lipoids and proteins of the brain and the solution of electrolytes under the microscope, we noted immediate activity of organization. Cell-like forms appeared and grew slowly (fig. 1). They multiplied, sometimes by budding, and sometimes by direct division (fig. 2). These cells were nucleated; they took vital stains; they consumed oxygen; they gave off carbon dioxide. Under a high power lens, free movement of granules and a movement not unlike the brownian movement were seen, and sometimes the movement was so rapid that it was difficult to keep the cells in the field of vision of the microscope. Some of these mixtures have continued to show active cells for two and one-half months.

Exactly the same technic was carried out for the other organs of animals. The lipoids and proteins of the various organs other than the

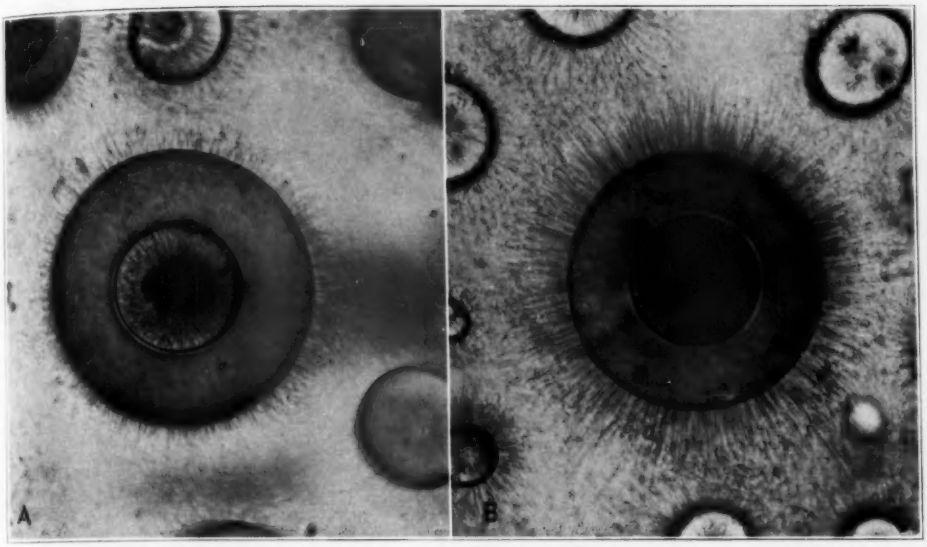

Fig. 1.—Photomicrographs of the same ciliated autosynthetic cell taken fifteen minutes apart: *A*, short and sparse cilia; *B*, long and abundant cilia.

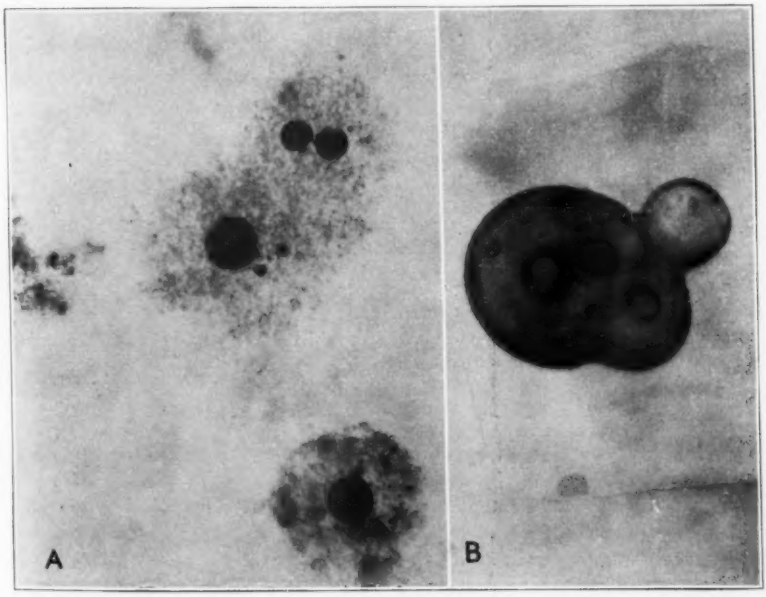

Fig. 2.—Division of autosynthetic cells by fission (*A*) and by budding (*B*). The cells shown in *A* were stained with hematoxylin-eosin.

brain were extracted and the ash was obtained; but on mixing the lipoids, proteins and a solution of the ash of these various organs, only feeble or no power of organization was seen. The nearest approach to organization in extracts from organs other than the brain was in the case of the spleen, and to a lesser degree of the ovary and the testes, but

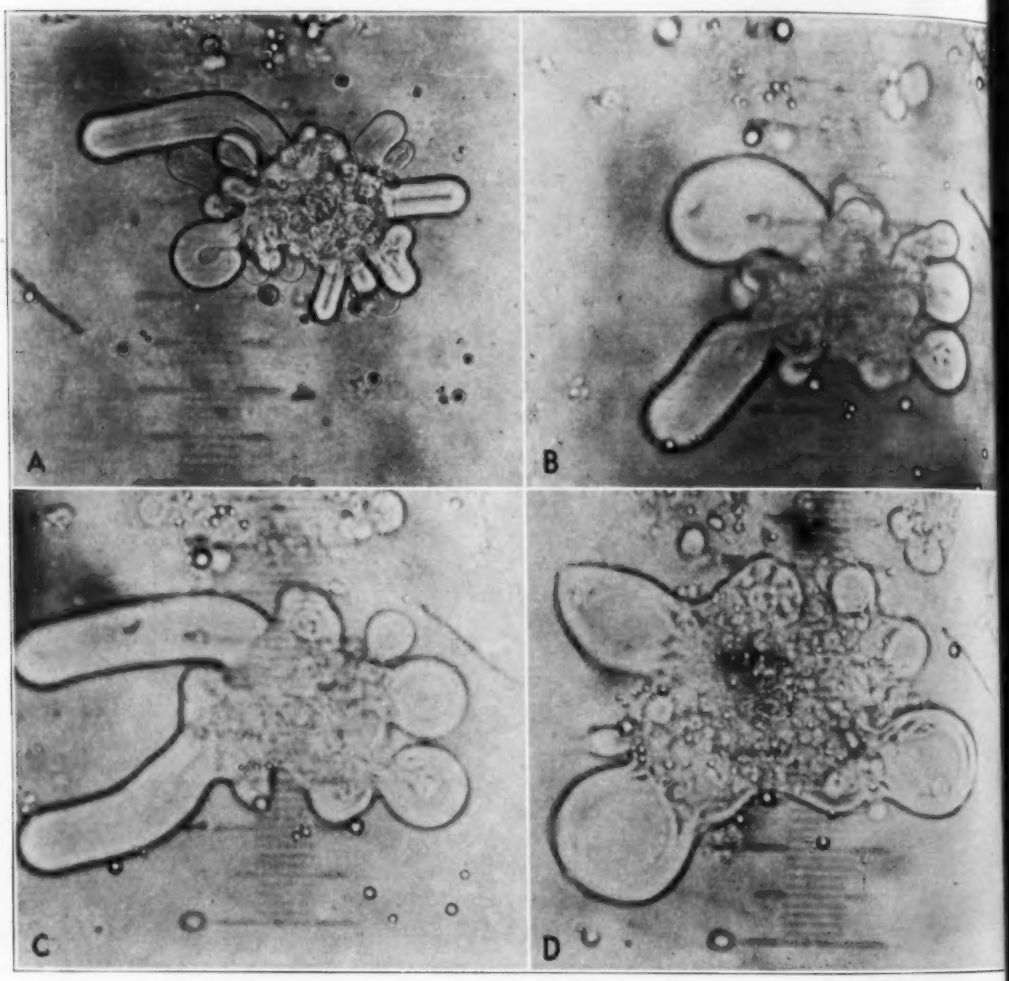

Fig. 3.—Successive stages in the growth and movement of an ameboid autosynthetic cell. Forty-eight photomicrographs of this cell were taken at intervals of fifteen minutes. The photomicrographs shown here were taken at the following intervals after *A*: *B*, one hour and forty-five minutes; *C*, four hours and forty-five minutes; *D*, eleven hours and thirty minutes.

the organization seen in these cases was not at all of the same order as that which took place in the mixture of the elements of the brain.

We next observed the effects of adding the lipoids of the brain to the proteins and solutions of the ash of each of the other organs. Immediate organization was observed. The cell-like structures that were

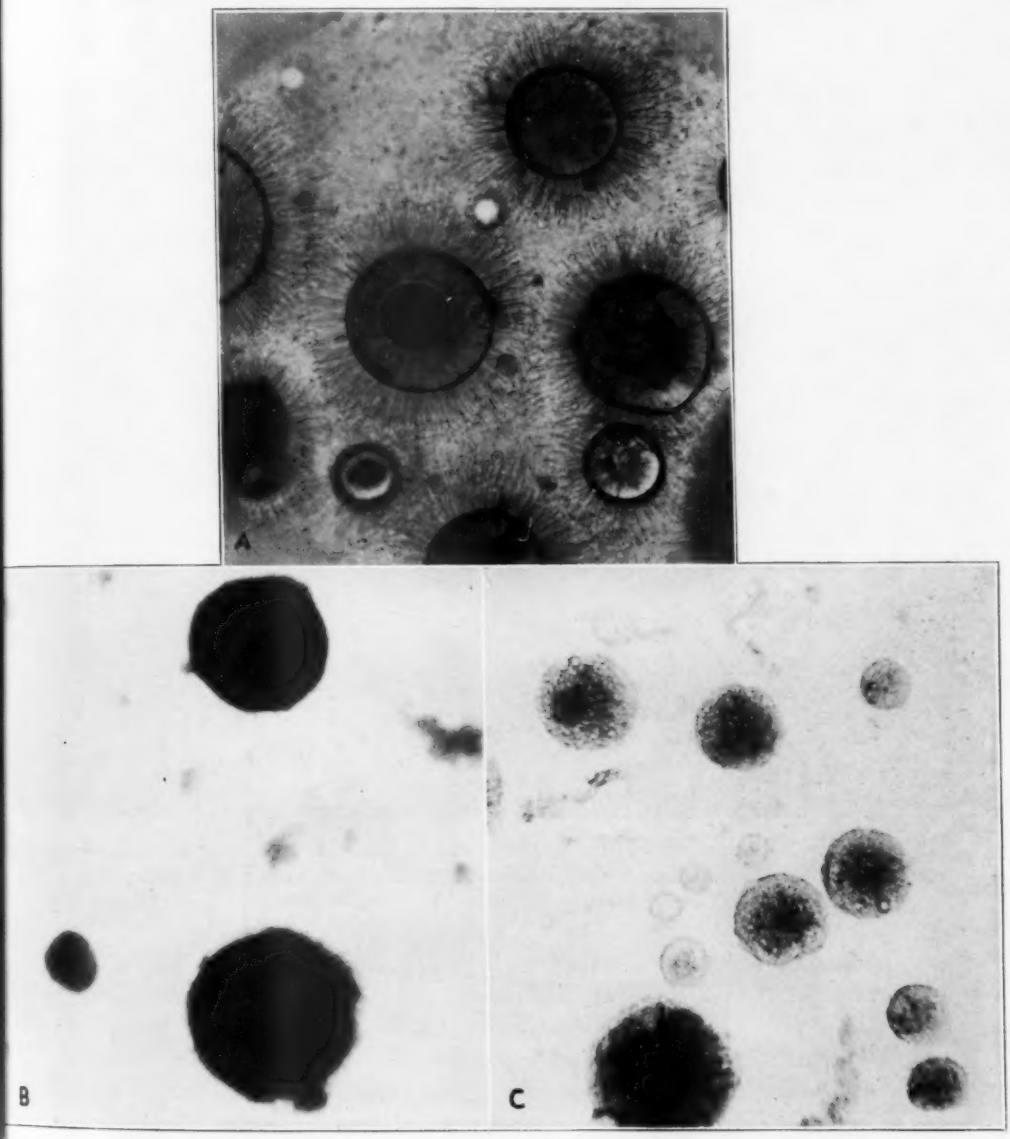

Fig. 4.—The effect of exhaustion on the formation of autosynthetic cells: *A*, normal autosynthetic cells; *B* and *C*, unorganized masses produced in the mixture of protein and electrolyte solution with *B* the lipoid extracted from the brain of a rabbit that died of exhaustion from insomnia, and (*C*) the lipoid extracted from the brain of a dog that had died from distemper.

formed took vital stains; they grew in size; they multiplied and showed respiration. This experiment revealed clearly that the lipoid of the brain is unique in being the possessor of a structure that has the power of organizing the proteins of any organ.

As we have stated, these autosynthetic cells took vital stains (fig. 2*A*). They grew and multiplied. They showed internal organization such as a nucleus, granules, etc. They varied considerably in size. They had respiration, their consumption of oxygen running as high as 14 mm.^{3} per hour per 2 cc. of cell mixture over a period of five hours, the respiratory quotient ranging from 0.7 to 0.98. Some of these cells were obtained for a period of nine hours, and many

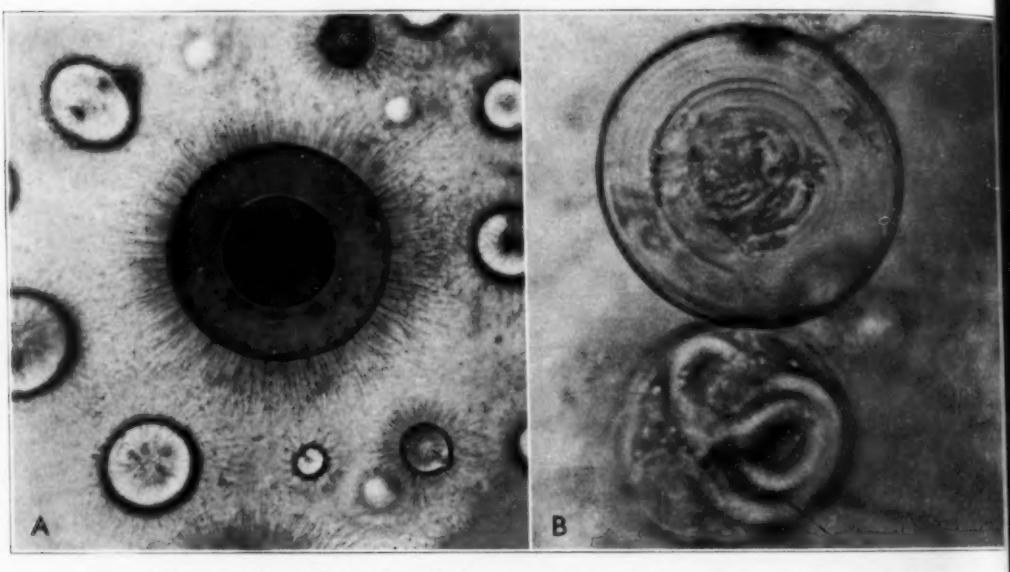

Fig. 5.—The effect of radiation on autosynthetic cells: *A*, normal autosynthetic cell; *B*, radiated autosynthetic cells. Note the unorganized masses of fat within the cell membranes.

photographs showing the changes in their form were taken. The form of the cells seemed to depend on the p_H of the electrolyte solution, ciliated cells being always produced in a solution of p_H 7.5.

While carrying out the effects of adding various "food" substances to the cells, it was found that dextrose increased the metabolism of the cells while the various culture materials such as beef broth, agar, blood serum, etc. showed little or no effect. It is necessary, however, in order to keep cultures alive over a period of time, to feed them by the occasional addition of protein. In one case suprarenal protein was added, and the cell immediately assumed the appearance of an ameba and pseudopodia like those of an active ameba were thrust out. Occa-

sionally the cell moved, apparently without first thrusting out pseudopodia, although the usual manner of movement was by the thrusting out of a loop of fiber-like substance from the body of the organism, into which loop the contents of the organism, the granules, etc., seemed to flow, the organism moving in the direction of the flow (fig. 3).

Of special significance was our observation that autosynthetic cells were not formed in the brain-lipoid-brain-protein, electrolyte mixture of dogs which had died from distemper. In rabbits that had died of exhaustion from insomnia, unorganized masses appeared in a mixture of this kind (fig. 4).

On the addition to the brain lipoids and proteins of an electrolytic solution identical with the brain ash solution, with the exception

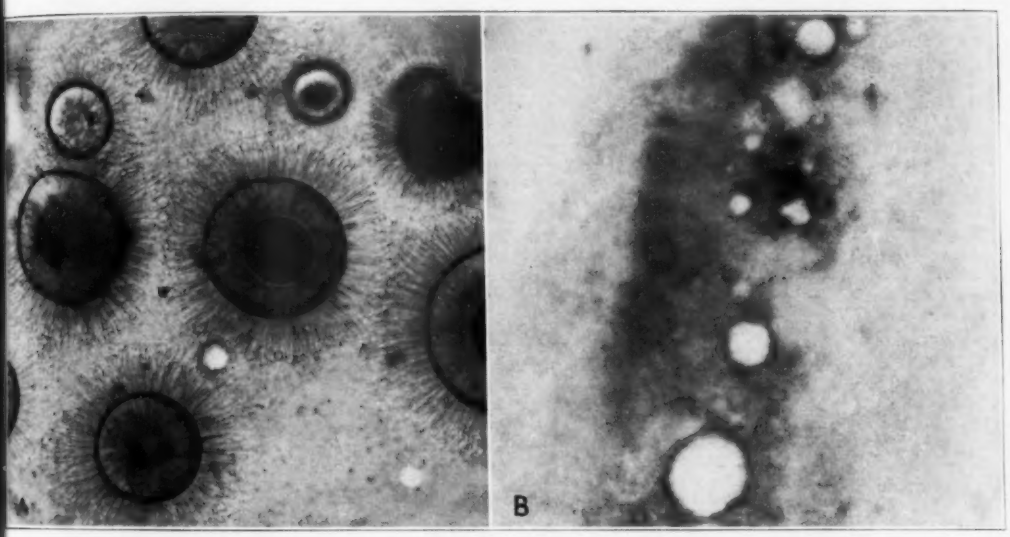

Fig. 6.—The effect of lack of oxygen (asphyxiation) on the production of autosynthetic cells: *A*, normal autosynthetic cells; *B*, lack of organization and fatty droplets in a mixture of electrolyte solution and protein with lipoids which had been shut away from the air for a number of weeks.

that the potassium salt was omitted, the formation of cells was delayed, and the cells differed in form from those found in the complete brain ash solution. It should be noted that the lipoids themselves held adsorbed potassium ions. Could all the potassium be eliminated, it might be that the organization of cells would be entirely inhibited.

In collaboration with Dr. Otto Glasser of the Cleveland Clinic Radiation Research Laboratory, we subjected the lipoids of the brain to intense radiation before they were mixed with the proteins of the brain and the electrolyte solution, and we found that the mixture had lost the power of organization—no cells were formed. The radiated lipoid

material assumed the aspects of a different substance. Small globules, apparently resembling neutral fat, appeared, suggesting that radium dislocates the metal elements, viz., the molecules of potassium and of phosphorus that bind together the delicately poised elements of the cell. Radiation of newly formed cells broke them down (fig. 5). On the other hand, radiating the protein had no effect. Autosynthetic cells

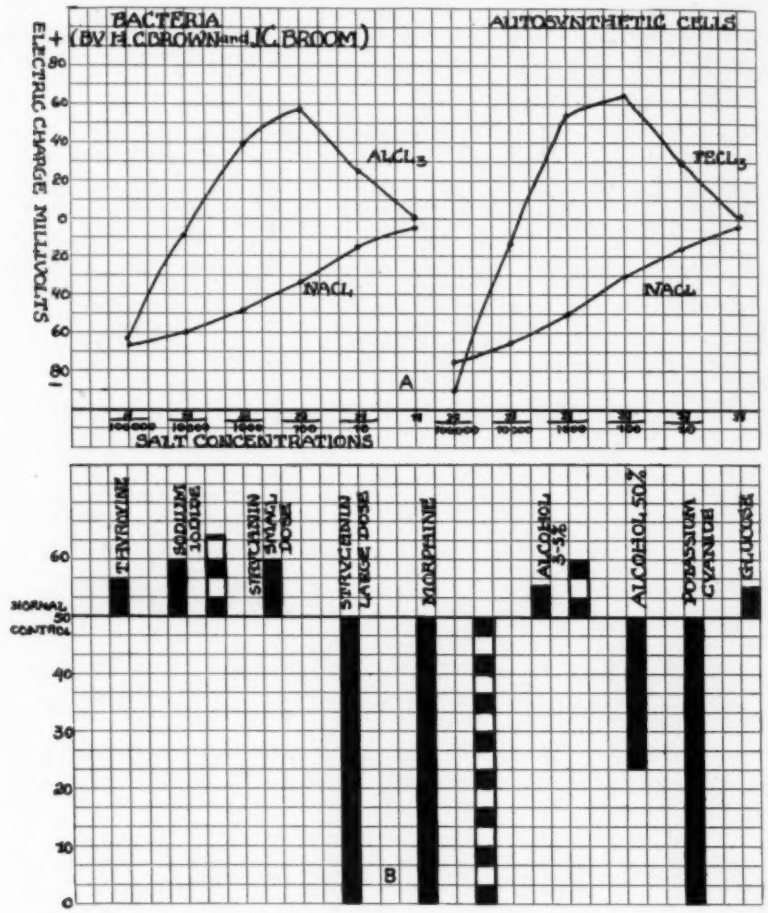

Fig. 7.—The potential difference of autosynthetic cells. *A* shows the effects of varying concentrations of sodium chloride and ferric chloride on the potential difference. Compare the curve for the autosynthetic cells with that for bacteria as established by Brown and Broom. *B* Shows the effects of various agents on the potential difference. (The potential difference of the cells was measured by cataphoresis; that of the ameba by a direct electromotive method.)

were formed with radiated protein and with nonradiated lipoid as freely as with nonradiated protein. It would seem that the lethal effect of radiation must be exerted on the lipoid element of cancer cells.

Cataphoretic measurements have been made from which the electric charge of the protein, of the lipoid and of the structures have been calculated. There was a marked potential difference between the lipoid and the protein, and the charge on the cells has been found to vary from 50 to 70 millivolts.

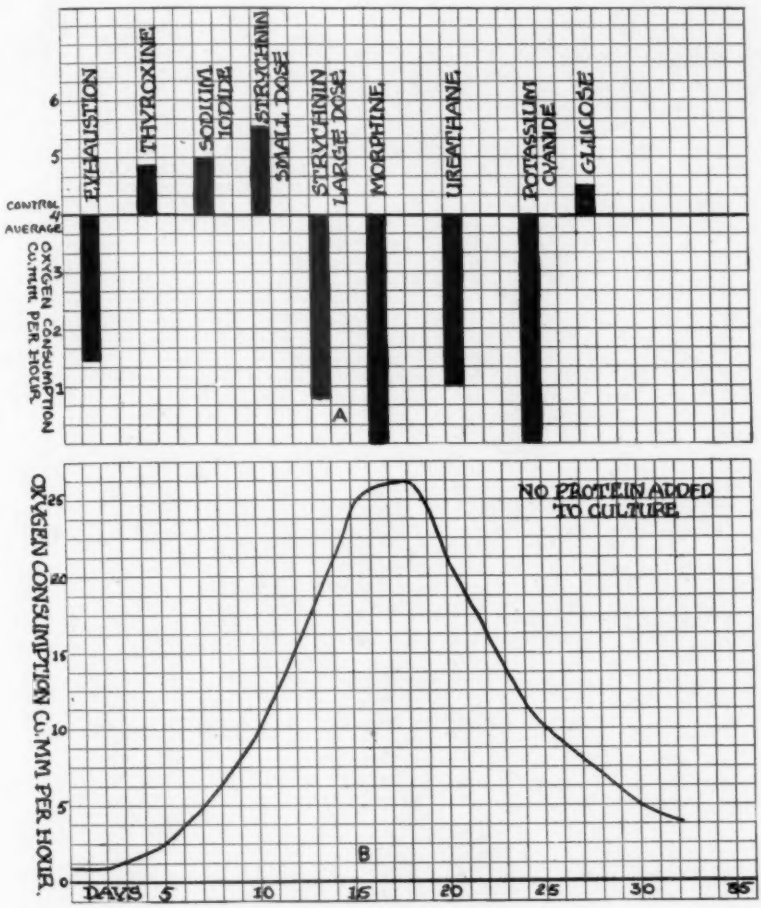

Fig. 8.—The oxygen consumption of autosynthetic cells: *A*, The effect of various agents on the oxygen consumption of autosynthetic cells; *B*, The progressive changes in the oxygen consumption of autosynthetic cells during thirty-four days.

Direct measurements of the electric potential difference of the cells and of the nucleus and cytoplasm were made by introducing electrodes into them. The nucleus was found always to be positive with relation to the cytoplasm, the difference of potential varying between 20 and 30 millivolts.

When "old lipoids," that is, when lipoid material that had been kept over a number of weeks and had been shut away from the air was used, we observed that instead of organized autosynthetic cells, fatty droplets were formed (fig. 6). These fatty droplets which were similar to those seen after the lipoid had been radiated were seen also after a cyanide was

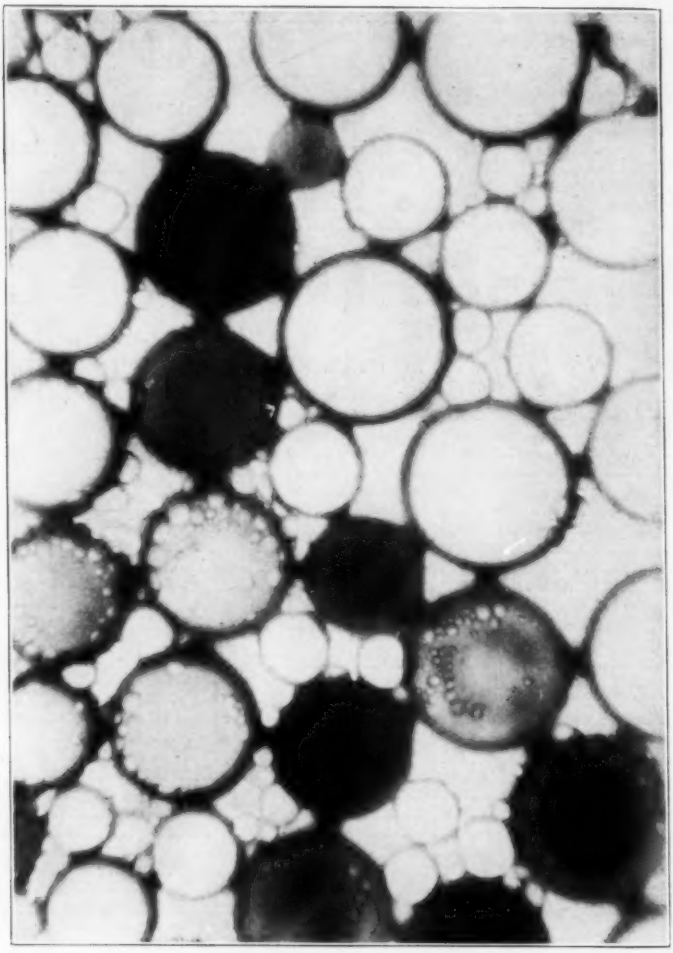

Fig. 9.—Unorganized masses produced in a mixture of electrolyte solution with the lipoid and protein extracted from a cancer.

added to the lipoid mixture and after the structures were deprived of oxygen, that is, asphyxiated. The phenomenon apparently corresponds to fatty degeneration.

The effects of the addition of various agents to the mixture of lipoid, protein and electroiyte were as follows: Both the potential difference

and the respiration were decreased on the addition of an anesthetic (urethan) (figs. 7 and 8). (Note: The effect of ether and of chloroform could not be tested as they immediately dissolved the lipoid.) The addition of salts in various concentrations affected the potential difference of our autosynthetic cells in a manner strikingly similar to the effect of the same concentrations on the potential differences of bacteria (Brown and

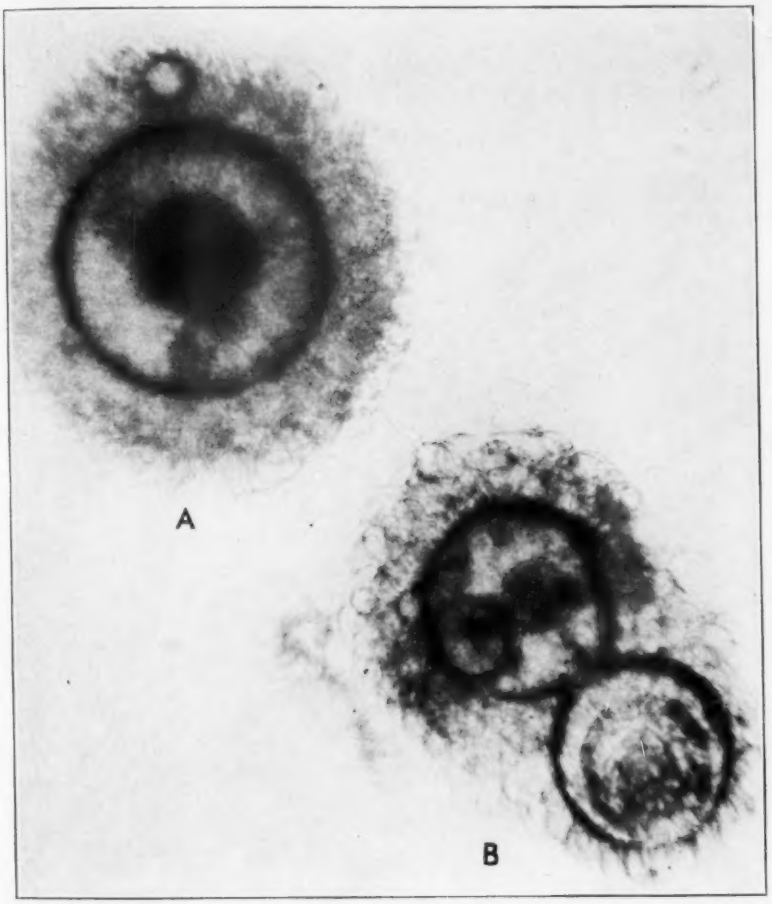

Fig. 10.—Autosynthetic cells produced in a mixture of electrolyte solution with the lipoids and proteins extracted from a human brain. Note the active division in progress in (*B*).

Broom) as is shown by the plotted curves in the chart. Both the potential difference and the respiration of the autosynthetic cells were increased on the addition of some agents. The potential difference and the respiration were decreased on the addition of morphine. On the addition of a small amount of strychnine or of alcohol (from 3 to 5 per cent), the

potential difference was increased. On the addition of large amounts of either strychnine or alcohol (50 per cent), the potential difference was decreased. On the addition of a cyanide or of a toxin, the potential difference was decreased to zero.

The lipoids and proteins extracted from a cancer, when mixed with a solution of the ash of the same cancer, did not produce cells, but a bizarre structure characterized by the appearance of many fatty droplets (fig. 9).

A mixture of the lipoids and proteins of a human brain with the electrolyte solution produced a highly organized cell with active division (fig. 10).

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